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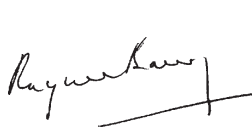
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As the analysis of recent decades clearly illustrates, science and technology are making exponential progress in all fields. This is particularly true of two areas: Information and Life Sciences, recognized as the keys to economic development and substantial changes in our lifestyle throughout the 21st century.

Health-related and food-related industries, like all sectors with an environmental component, are finding themselves increasingly influenced, and indeed transformed, by the progress made in life sciences.

Since its inception, BioVision has addressed many of the vital life sciences issues facing our world today, and has achieved much of what it initially set out to accomplish: mobilise foremost specialists along with policy makers, researchers, consumer representatives, patients' associations, NGOs and the media, with the aim of fostering open debate and exchange between Science, Society at large and Industry.

The unique concept of The World Life Sciences Forum BioVision was born in Lyon and will continue to thrive thanks to support from the Ville de Lyon, Grand Lyon, Département du Rhône, and the Région Rhône-Alpes.



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Preface

Since its inception in 1999, The World Life Sciences Forum BioVision has played a vital role in promoting the sustainable development of Life Sciences on an international level, ensuring that they remain beneficial to humankind and the environment, and committed to ethics.

BioVision has established itself as a platform for dialogue and debate by engaging top stakeholders and policy makers from *Science*, *Society* and *Industry* in discussions of what science can do, what society is willing to accept, and what industry can produce, all within a sound ethical framework. BioVision 2005 casts current and future issues in life science within the three inter-dependent sectors of *Health*, *Agriculture* and *Environment*.

The BioVision debate seeks to:

- Explore major topics, identify disagreements, and reach consensus when possible.
- Identify existing opportunities and facilitate their implementation to benefit both developed and developing countries.
- Promote positive action to define priorities, identify precautionary principles, and create a path to future success.
- Build a sustained communication flow around key issues, ensuring that they are understood and shared by stakeholders and the society.

These new BioVision volumes could not have materialized without the essential contributions of a wide range of people. Special thanks are due to the BioVision Lyon team organizing and implementing BioVision 2005. Dominique Lecourt and Ben Prickril assisted in preparing introductory materials for these volumes. David Zavaglia, Christine Toutain, Cécile Trespeuch, Anne-Sophie Bretonnet, Sandra Zoghbi, and Laurence Clement of BioDocs (www.biodocs.net/lyon) prepared the reference materials. The *Syntheses and Recommendations* were prepared with the expert assistance of Pierre Anhoury, Jens Riese, Oskar Slotboom, Clare Cockcroft, and Radhika Bhattacharya. Daniel Leclercq has been extremely helpful in moving the books from concept to fruition. Frank Weinreich and his colleagues at Wiley-VCH

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have been exemplary in putting together the entire volumes, including transcription and editing of the presentations.

Special appreciation is due to the truly outstanding group of BioVision 2005 Chairs, all of whom have graciously donated their considerable skills to formulating and implementing the Forum.

Lyon, October 2005

Philippe Desmarescaux
Chairman and Founder
The World Life Sciences Forum BioVision

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Module I

Is the Investment in New Therapies Paying Off?

Introduction

*Dominique Lecourt**

Progress in biomedical research has advanced rapidly in recent years. This has contributed to better understanding of diseases, new therapeutic options, and improvement in both length and quality of life. The contributions of genetics to the study and treatment of cancer illustrates this wonderfully. Recent research reveals genetic mechanisms, particularly in the early stages of development of cancer cells. As for traditional therapies (surgery, chemotherapy, radiotherapy), new strategies based on molecular targets have shown high efficacy with minimal side effects.

But are such innovations economically profitable? The example of the development and use of vaccines for diseases like variola or measles makes it possible to understand the nature of the problem. Beyond the immediate calculations of cost-benefit ratios there is an excellent argument that children growing up in good health will contribute to the future economic development of their countries. If poor countries are not solvent today isn't there a means of enabling them to improve this situation for tomorrow? This promotes the idea that the 21st century will be the "century of the vaccines".

However, in order to succeed, neither research nor good intentions will suffice. Innovation must be supported by dynamic partnerships between public and private research organizations, and between academic researchers and biomedical industries. Governments and other decision makers understand implicitly the need for robust health systems, effective organization of markets and adequate regulatory structure to support innovation and the diffusion of progress through all levels of society.

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General Delegate of the Biovision/Academy of Science Foundation.

Author Biography

Zhu Chen



Vice President, Chinese Academy of Sciences

Prof. Zhu Chen obtained his master's degree at Shanghai Second Medical University in 1981 and doctor's degree at Paris VII University in 1989, and presently is member and Vice President of the Chinese Academy of Sciences, a Foreign Associate of the National Academy of Sciences of the USA, Titular Member of European Academy of Arts, Sciences and Humanities, Co-Chair of InterAcademy Panel, Director of the Chinese Human genome center at Shanghai and Director of the Shanghai Institute of Hematology. He is devoted to research on leukemia, in the field of which he is well-known for the advancement of molecular target-based therapy of human cancer after the breakthroughs in the clinical and molecular study of the treatment of acute promyelocytic leukemia with all-trans retinoic acid and arsenic trioxide. He is also now playing a leading role in human genome project of China. Zhu Chen was the first non-French winner of "Prix de l'Oise" by "La Ligue Nationale contre le Cancer" of France. In October 2002, he was awarded the "Chevalier de l'Ordre National de la Légion d'Honneur".

1

New Frontiers in Cancer Treatment

Zhu Chen

1.1

Introduction

Cancer is a most notorious disease which causes widespread mortality and morbidity on a worldwide basis. Moreover, the harm caused by cancer to society is becoming increasingly serious. When considering the history of disease mortality in developed countries it can be seen that, about 100 years ago in the USA for example, cancer was the cause of death in only 3.7% of the population. However, by 1997 it was responsible for 23% of all deaths in the USA, and was ranked number two among the leading causes of mortality. Likewise, in China – a developing country with a booming economy and a rapidly changing lifestyle – there has been a significant increase in mortality due to cancer over the past two decades (Figure 1.1). For example, in 1982 cancer was the third highest cause of death among the Chinese population, but today it is the leading cause.

In continuing the fight against cancer, it is essential to understand the major biological features of cancer cells. These cells differentiate themselves from normal cells in several ways: a significant growth advantage caused by uncontrolled cell division and the arrest of differentiation and maturation; a deregulated cell death leading to an accumulation of malignant cells; and an ability to invade surrounding tissues and to metastasize to new body sites (Figure 1.2).

Clinically, different stages of disease progression can be either observed or detected, from precancerous status to localized tumor to regional tumor and to metastasis. Since the 1970s, two types of gene have been identified as being implicated in the oncogenetic process. A large body of evidence suggests that loss of function in tumor suppressor genes and gain-of-function mutations in oncogenes categorize most, if not all, human cancers. On occasion, genetic abnormalities can occur at a juvenile level, and this gives rise to a predisposition

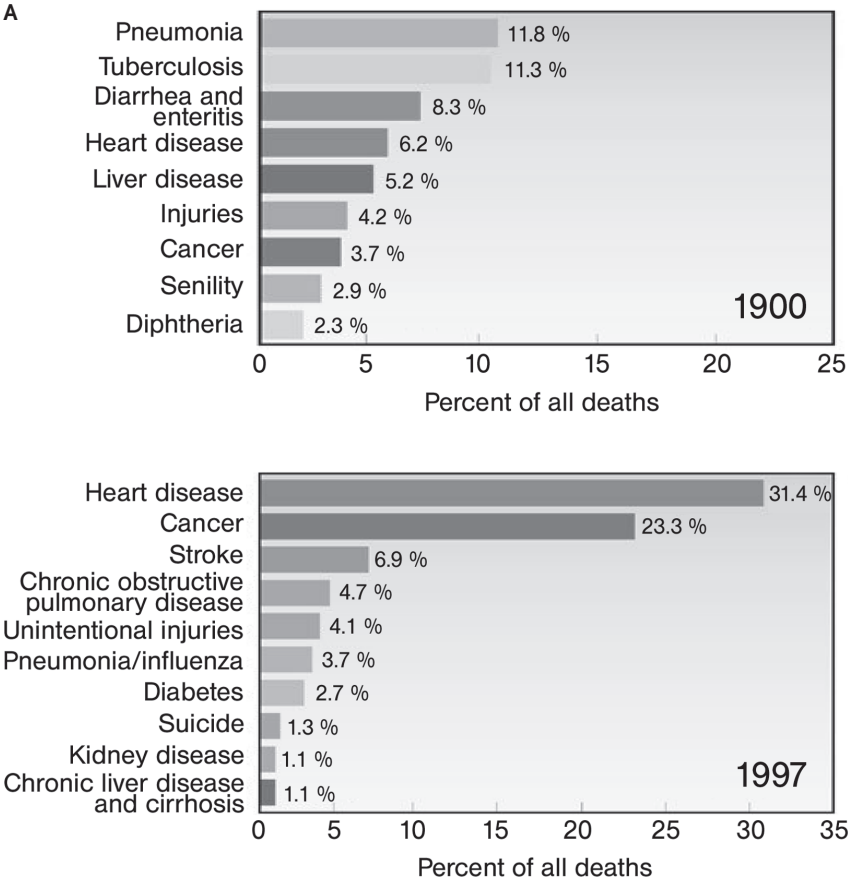


Figure 1.1 Contribution of cancer to human mortality.
(A) Leading causes of death in the USA.
Source: Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System and unpublished data (data from 1900 do not represent all states).

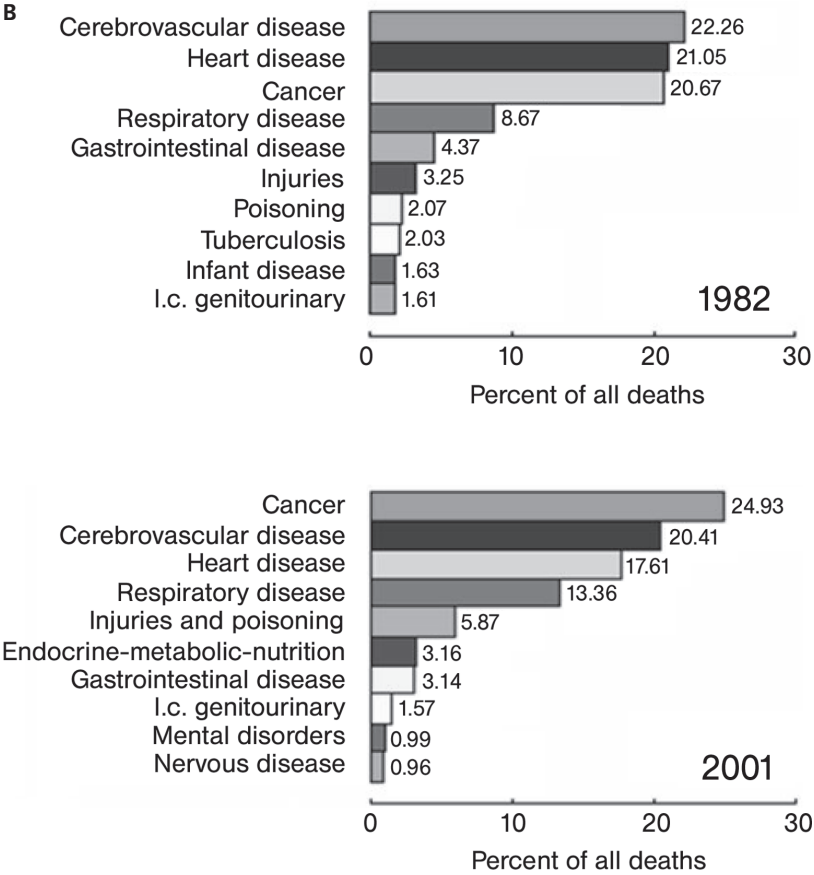


Figure 1.1 (Continued)
(B) Leading causes of death in China (data are from Chinese cities).

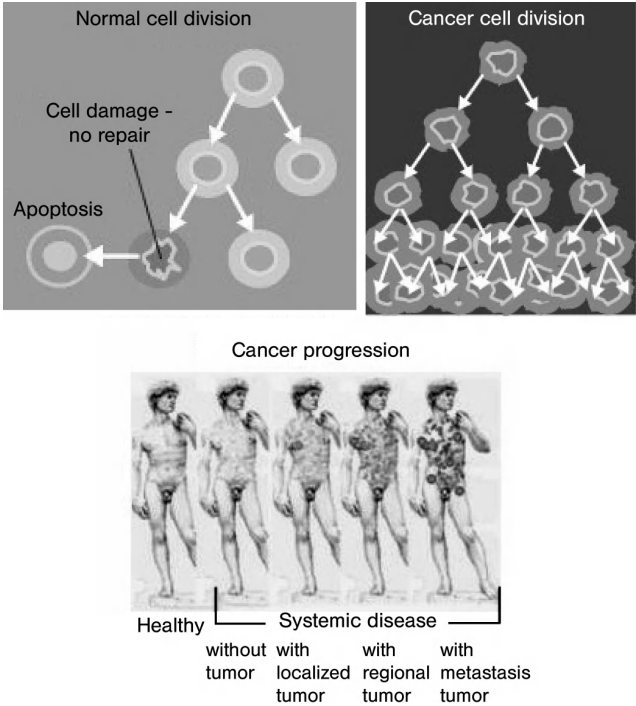


Figure 1.2 Cancerogenesis and progression. Malignant neoplasms are characterized by the proliferation of anaplastic cells that tend to invade surrounding tissue and metastasize to new body sites.

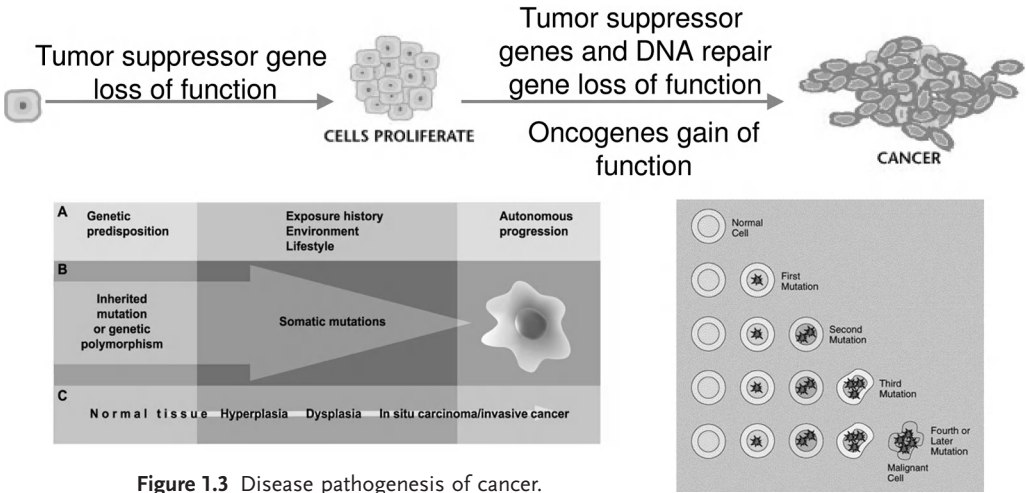


Figure 1.3 Disease pathogenesis of cancer. (A) Factors contributing to the generation of the cancer cell. (B) The effects of these factors on the cell. (C) The pathologic outcome of (A) and (B), with the progression from normal tissue to invasive carcinoma highlighted.

to cancer. Nevertheless, in most cases the cancer is associated with somatic mutations as a result of an interaction between environmental factors and genetic information (Figure 1.3). An accumulation of gene mutations has been shown to accompany disease progression underlying an increased degree of malignancy.

1.2

Cancer Treatment

Conventionally, cancer was treated either surgically, or by chemotherapy and/or radiation therapy. These therapies have evolved over time, with surgery having now become more precise and less invasive.

Although chemotherapy was first developed during the mid-1940s, since the 1960s the combined use of drugs such as antimetabolites, alkylating agents, topoisomerase inhibitors and anticancer antibiotics has greatly improved the efficacy of chemotherapy (Table 1.1). Likewise, sophisticated instruments have been developed to enhance the effect of radiation therapy. Despite these improvements, however, the outcome of conventional cancer therapy remains far from satisfactory. Unfortunately, neither chemotherapy nor radiotherapy is able to distinguish normal cells from cancer cells, and consequently these agents will not only kill cancer cells but will also cause damage to normal cells and tissues. In clinical terms, the toxicity of these therapies often reaches the maximum tolerated by the organism.

Some cancers are insensitive to both chemotherapy or radiotherapy, however, and consequently new concepts of cancer therapy require the global decoding of genetic information. This will allow the genome-wide characterization of molecular abnormalities in cancer which, in turn, will permit the development of new therapeutic strategies. In fact, this was the initial motivation, some 19 years ago, for the Human Genome Project to be initiated.

Following completion of the Human Genome Project, and the near-completion of the SNP haplotype, a new project was recently launched to address the cancer genome. Recent advances have shown cancer to be a disease which involves dynamic changes in the genome and, indeed, it is estimated that about 600 genes are involved in the process of oncogenesis (Figure 1.4). These genetic events confer cancer cells with a self-sufficiency of growth signals, an insensitivity to antigrowth signals, a capability to evade apoptosis, a limitless replicative potential, sustained angiogenesis, and properties of tissue invasion and metastasis. Clearly, the elucidation of the genetic basis of cancer will not only shed new light on carcinogenesis, but also provide novel therapeutic perspectives (Figure 1.5).

Table 1.1 The history of chemotherapy (1942 to present).

Year	Event
1942	Louis Goodman and Alfred Gilman use nitrogen mustard to treat a patient with non-Hodgkin's lymphoma and demonstrate for the first time that chemotherapy can induce tumor regression.
1948	Sydney Farber uses antifolates to successfully induce remissions in children with acute lymphoblastic leukemia (ALL).
1955	The National Chemotherapy Program begins at the National Cancer Institute (NCI), a systematic program for drug screening commences.
1958	Roy Hertz and Min Chiu Li demonstrate that methotrexate as a single agent can cure choriocarcinoma, the first solid tumor to be cured by chemotherapy.
1959	The Food and Drug Administration (FDA) approves the alkylating agent cyclophosphamide.
1965	Combination chemotherapy (POMP regimen) is able to induce long-term remissions in children with ALL.
1970	Vincent DeVita and colleagues cure lymphomas with combination chemotherapy.
1972	Emil Frei and colleagues demonstrate that chemotherapy given after surgical removal of osteosarcoma can improve cure rates (adjuvant chemotherapy).
1975	A combination of cyclophosphamide, methotrexate and fluorouracil (CMF) was shown to be effective as adjuvant treatment for node-positive breast cancer.
1978	The FDA approves cisplatin for the treatment of ovarian cancer, a drug that would prove to have activity across a broad range of solid tumors.
1989	The NCI introduces 'disease-oriented' screening using 60 cell lines derived from different types of human tumor.
1992	The FDA approves paclitaxel (Taxol), which becomes the first 'blockbuster' oncology drug.
2001	Studies by Brian Druker lead to FDA approval of imatinib mesylate (Gleevec) for chronic myelogenous leukemia, a new paradigm for targeted therapy in oncology.
2004	The FDA approves bevacizumab (Avastin), the first clinically proven anti-angiogenic agent, for the treatment of colon cancer. Researchers at Harvard University define mutations in the epidermal growth factor receptor that confer selective responsiveness to the targeted agent gefitinib, indicating that molecular testing might be able to prospectively identify subsets of patients that will respond to targeted agents.

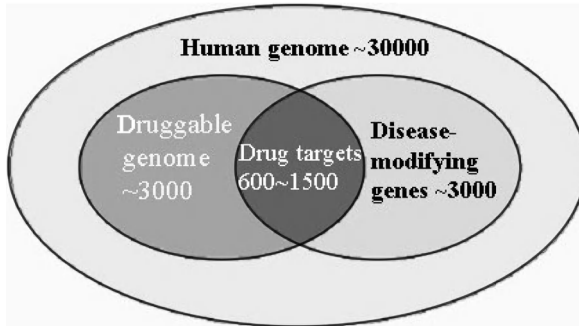


Figure 1.4 The impact of genomics.
(Source: Hopkins and Groom, *Nature Rev. Drug Discov.* 1, 727, 2002).

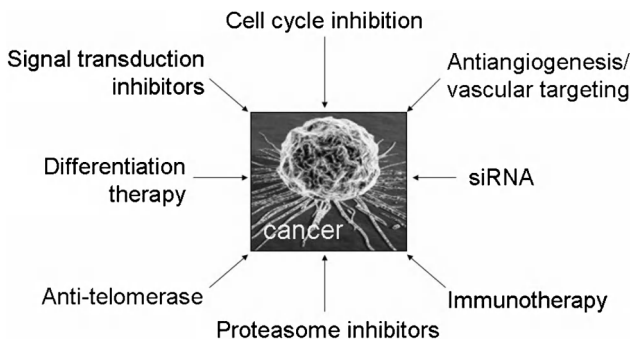


Figure 1.5 Treatment of cancer in the era of genomic medicine.

1.3 Target-based Therapies

Recently emerging anticancer strategies have been mainly based on “molecular target-based therapy”. The target chosen is critical to the malignant phenotype, but is not expressed in vital organs and tissues, thereby conferring a high efficacy with minimal adverse effects. The first examples of targeted therapy were provided by breakthroughs in the hematological setting (Figure 1.6). For example, leukemia is not a single disease but rather a group of diseases including myeloid and lymphoid leukemia subtypes; these can be further divided into acute and chronic subtypes. Importantly, specific gene mutations such as chromosome translocations and point mutations have been identified as playing a key role in leukemogenesis, thus providing potential targets for specific treatment to be developed. The first opportunity to develop a novel type of leukemia therapy arose during the mid-1980s, at the Shanghai Institute of Hematology.

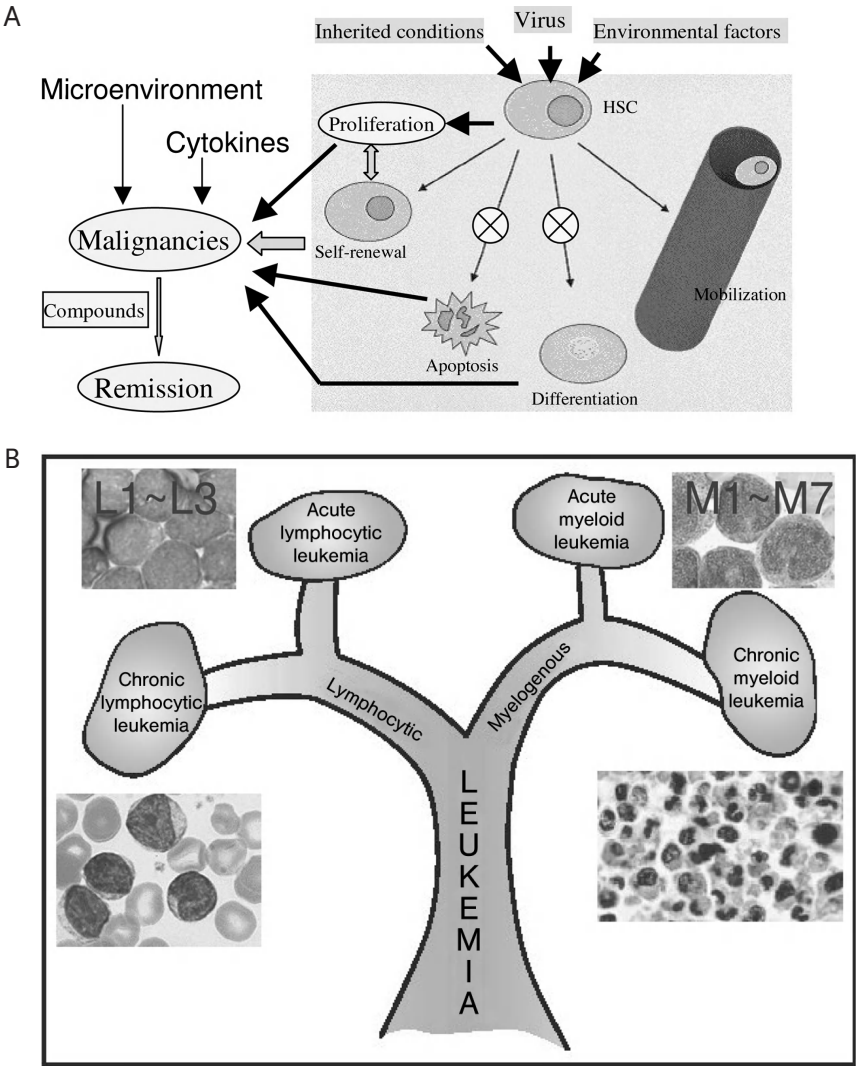


Figure 1.6 Developing targeted therapies. (A) General mechanisms for hematopoietic malignancies. (B) Leukemia tree (modified after M. Patlak).

1.3.1
Differentiation Therapy

In differentiation therapy – which in China is referred to as “educational therapy” – the approach is to educate the malignant cells to restore their normal program of differentiation and maturation, rather than to kill them (Figure 1.7).

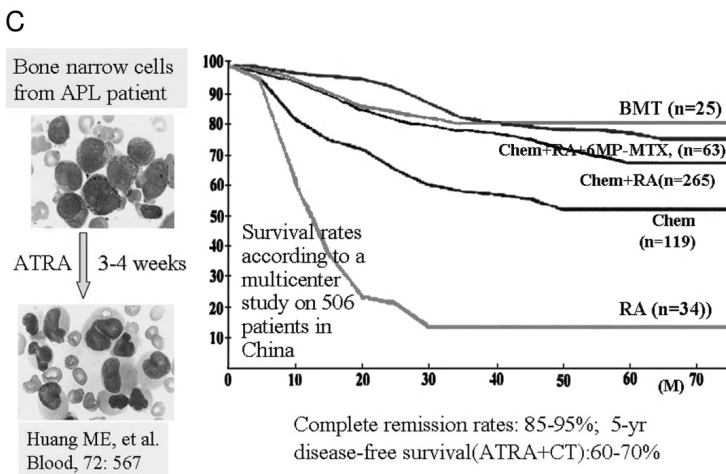
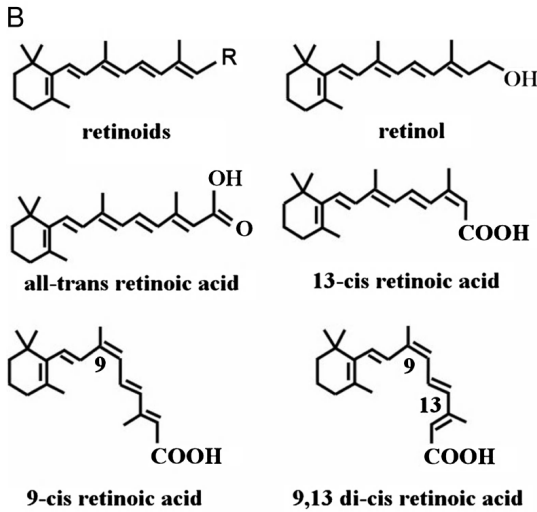
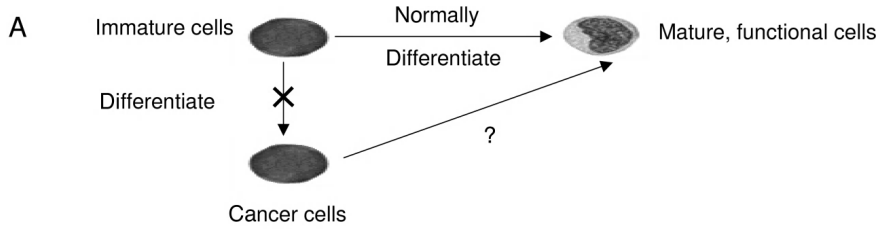


Figure 1.7 Differentiation therapy: from hypothesis to practice.

(A) The concept of differentiation therapy.

(B) Agents used in differentiation therapy.

(C) Treatment of acute promyelocytic leukemia with retinoid combination therapy.

(After Huang et al., Blood 72, 567–572, 1988).

In this approach, the differentiation inducers used are active metabolites of vitamin A, the retinoic acids, and the disease model for differentiation therapy is acute promyelocytic leukemia (APL). It was found that one isomer of retinoic acid – all-*trans* retinoic acid – could induce the differentiation of APL cells both *in vitro* and *in vivo*, and a complete remission rate of up to 90% could be achieved using all-*trans* retinoic acid (ATRA) alone. More importantly, five-year survival rates of about 50% have been reported by groups in China and in other countries with post-remissional therapy incorporating retinoic acid and chemotherapy. It appears that, to date, these are the best results achieved for the treatment for acute leukemias in adults. Subsequently, it was demonstrated by several groups that the leukemogenic fusion protein PML-(promyelocytic leukemia) RAR α (retinoic acid receptor alpha) is the result of a specific chromosome translocation t(15;17) and is the drug target for all-*trans* retinoic acid. All-*trans* retinoic acid is able to bind to the ligand-binding domain of the fusion receptor and recruit the nuclear receptor co-activator complex, thereby increasing transcription activation of the retinoic acid target genes necessary for granulocytic differentiation (Figure 1.8). Simultaneously,

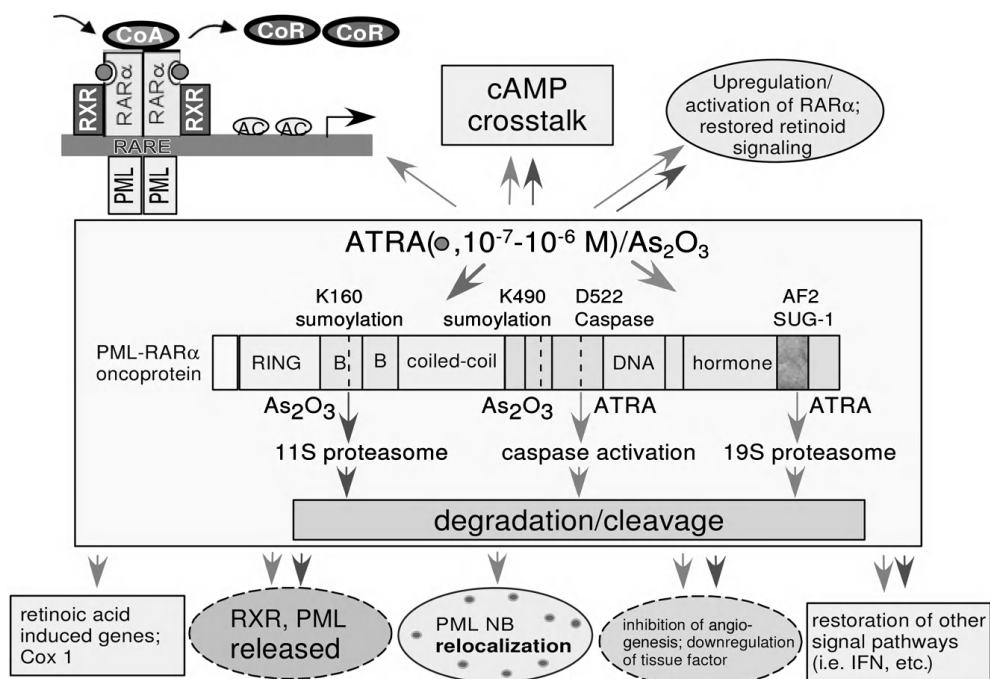


Figure 1.8 All-*trans* retinoic acid treatment for acute promyelocytic leukemia: a paradigm of targeted leukemia therapy 3.

it also induces proteasome-mediated protein degradation of the aberrant retinoic acid receptor, releasing the wild-type RAR α heterodimer, as well as the PML proteins required for granulocytic differentiation and apoptosis.

1.3.2

Arsenic Trioxide

A second breakthrough in the treatment of APL was the rediscovery of an ancient drug, arsenic trioxide, as an antileukemia remedy (Figure 1.9). Arsenic exerts a dual effect on APL cells, inducing differentiation at low concentrations but apoptosis at relatively high concentrations. In fact, even in relapsed patients who have received all-*trans* retinoic acid and chemotherapy, arsenic can achieve a complete remission rate of 80%, which suggests that it has a unique mechanism of action (Figure 1.10).

It was subsequently discovered that arsenic could modulate and induce degradation of the oncoprotein PML-RAR α , with the mode of action being quite different from that of retinoic acid. Others later showed that arsenic targets the PML moiety of the fusion receptor, with degradation of the PML-RAR α being mediated through sumoylation of the PML. Based on these findings, it was proposed five years ago that all-*trans* retinoic acid and arsenic might have a synergistic effect in APL as they target the same key protein in leukemogenesis, albeit via distinct mechanisms. Indeed, at the cellular level these two agents have strong synergy in inducing degradation of the PML-RAR α protein, as compared to all-*trans* retinoic acid (ATRA) or arsenic monotherapy. More importantly, the use of both drugs during remission induction and post-remissional therapy has yielded a much better molecular and a disease-free survival than in patients treated with a single agent (Figure 1.11).

This was, in fact, the result published a year ago, when no relapse was observed with a median follow-up of 18 months in a group of 20 patients treated with combination therapy as compared to monotherapy groups, where relapse occurred in a significant proportion of the patients. Whilst in biomedicine 100% relapse is not achievable, the most recent data showed that, among 45 patients with a median follow-up of 30 months, only two relapsed, and one of these subsequently responded to combination therapy. Thus, both the overall survival and disease-free survival rates were significantly better than the monotherapy groups in a comparable historic control group, and consequently it is believed that, for most APL patients, there is now hope of an effective cure.

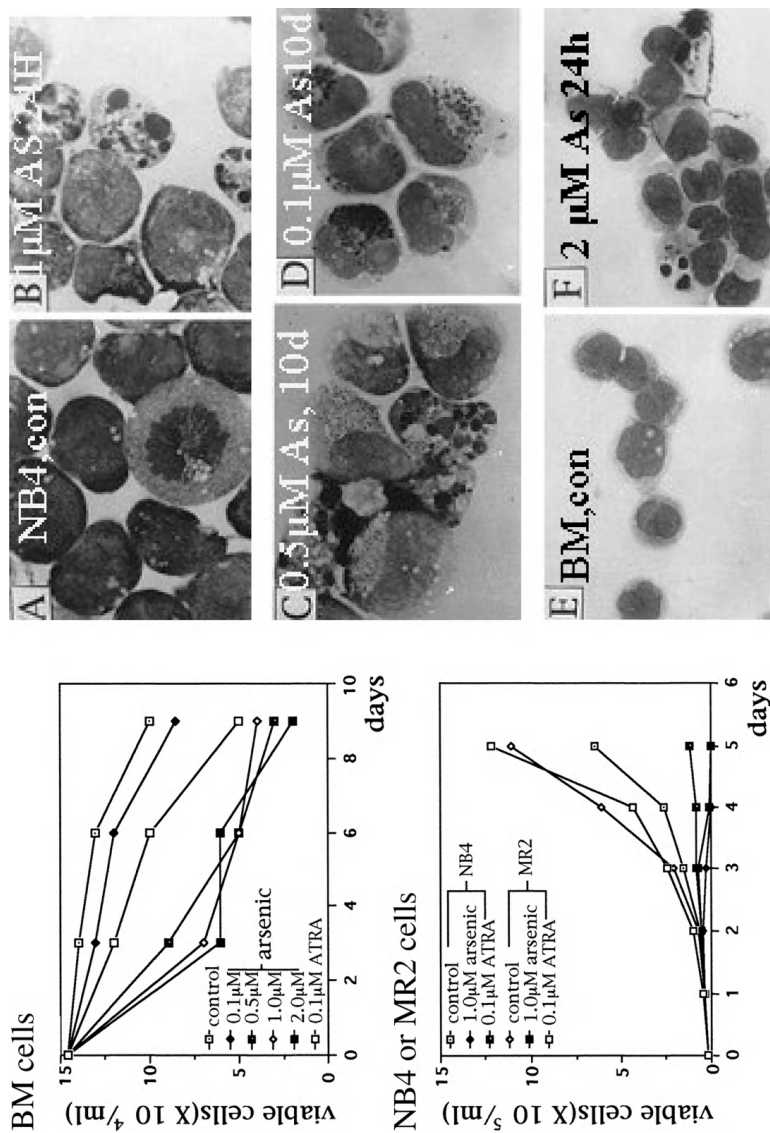


Figure 1.9 Arsenic trioxide as treatment for acute promyelocytic leukemia. (Source: Chen et al., Blood 89, 3345–3353, 1997).

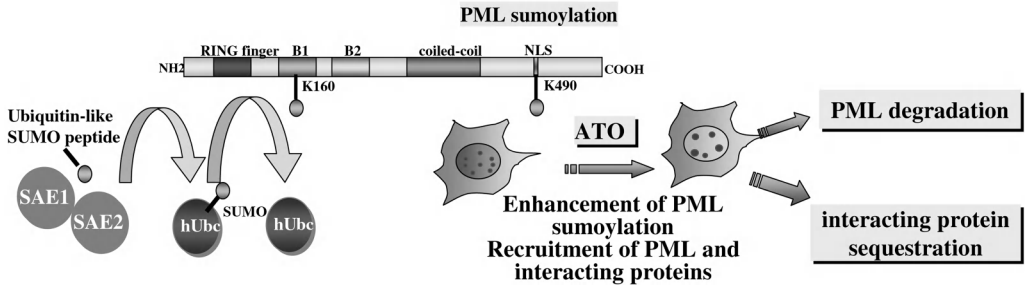


Figure 1.10 Mechanism of action of arsenic trioxide (ATO) on promyelocytic leukemia (PML) protein.

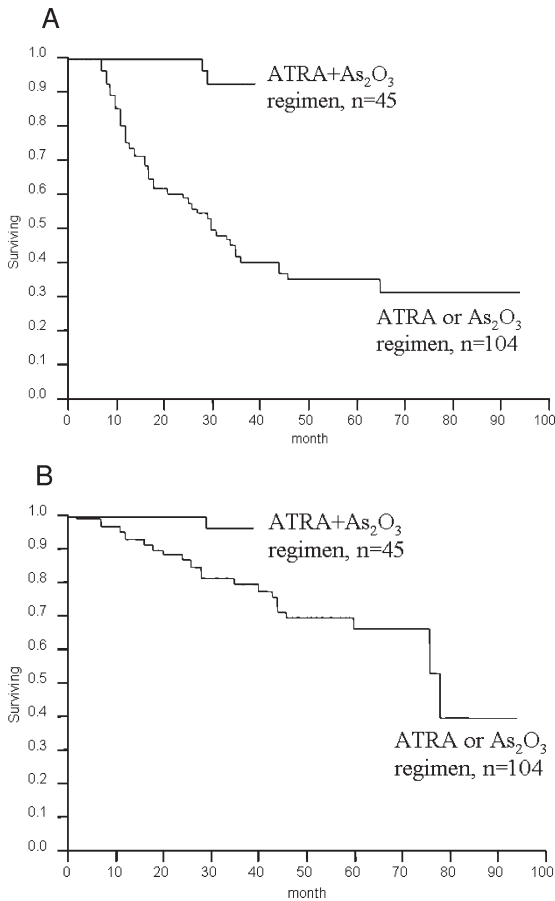


Figure 1.11 Survival rates after acute promyelocytic leukemia (APL) combination therapy. (A) Relapse-free survival. (B) Overall survival.

1.3.3

Imatinib

Another excellent example of target-based therapy is that of imatinib (Glivec, Gleevec®) in the treatment of chronic myeloid leukemia (CML). This condition is characterized by the presence of the Philadelphia chromosome which generates the PCR-ABL oncoprotein with abnormally increased protein tyrosine kinase (PTK) activity. Imatinib is able to bind in the ATP-binding pocket in the kinase domain of the ABL protein, and thus inhibits PTK activity (Figure 1.12).

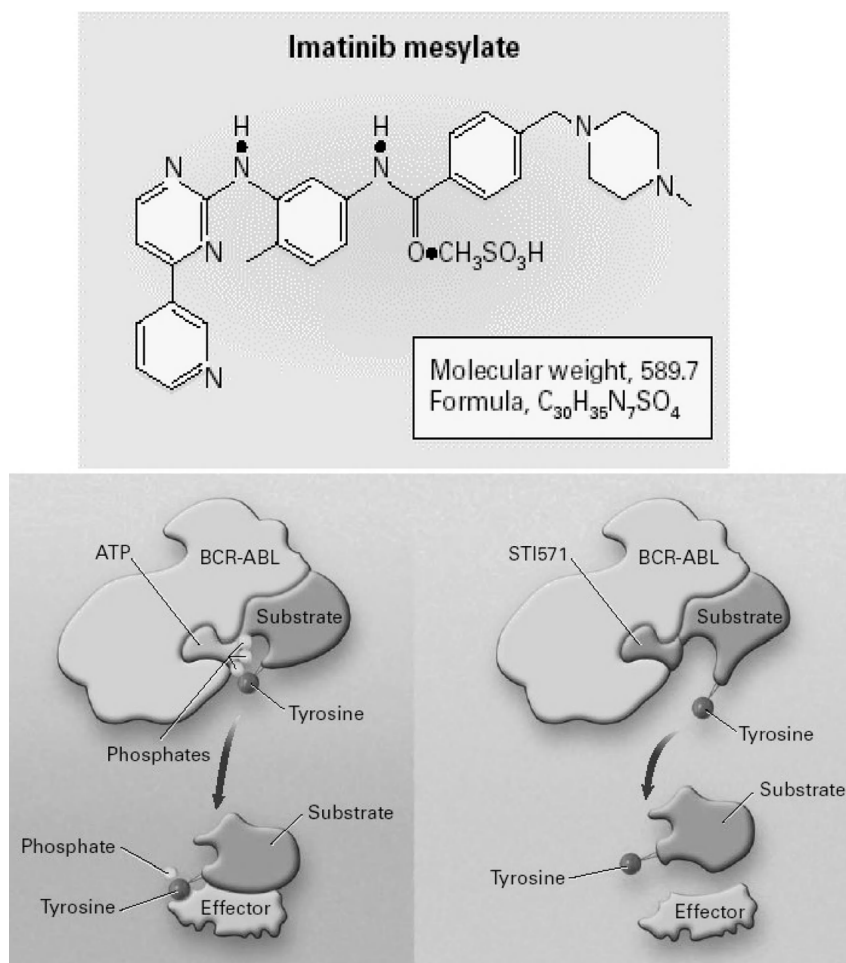


Figure 1.12 Imatinib: a protein kinase inhibitor in the treatment of chronic myeloid leukemia.

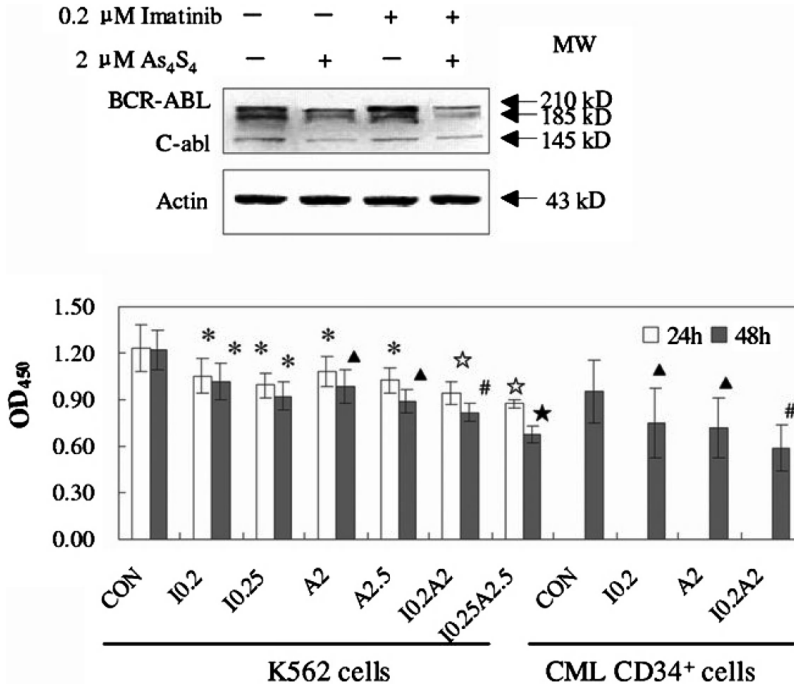


Figure 1.13 Synergistic targeted therapy of chronic myeloid leukemia with arsenic (A) and imatinib (I).

Today, imatinib is the new “gold standard” in CML therapy, and provides durable clinical cytogenetic and molecular remission in CML patients, particularly those in the chronic phase. However, with long-term use of imatinib, some patients develop resistance to the drug. According to investigations with APL, it is believed that a combination therapy might be more effective than single-agent therapy, even in the case of imatinib. A review of the literature showed that one drug which might, potentially, be combined with imatinib is arsenic sulfide. This differs from arsenic trioxide in that it exhibits a synergistic effect by inducing cell apoptosis with imatinib (Figure 1.13). The apoptosis is much more profound in cells treated with both agents than in those treated with a single drug. It was subsequently found that arsenic sulfide could significantly reduce the level of BCR-ABL protein (see Figure 1.13, upper panel), whereas imatinib inhibits the PTK activity of the oncoprotein. Interestingly, when the two drugs operate together, the reductions in BCR-ABL oncoprotein level and PTK activity are much more significant than with monotherapy. There is therefore, another paradigm of synergistic targeting therapy, not on a transcription factor such as PML-RAR α but on a signaling molecule, the BCR-ABL. The results obtained in clinical trials using combination therapy have so far been intriguing, however.

The mechanism of leukemogenesis remains elusive, however. In acute myeloid leukemia (AML) with major chromosome abnormalities, the molecular mechanisms have been well characterized, but in AML without identifiable chromosome abnormalities very little is still known about these mechanisms. The same is true for the acute transformation of CML. In order to further dissect the mechanisms of leukemogenesis and to open new therapeutic perspectives, the Shanghai Institute of Hematology recently launched the Leukemia Genome Anatomy Project (LGAP) to survey abnormalities in genes critical to the regulation of hematopoiesis and onset of leukemia. This project is accompanied by the Leukemia Integrative Chemical Genomics Project, which aims to facilitate target validation and compound screening. In fact, this is mostly based on the screening of natural compounds from traditional Chinese medicine.

Although surgery remains the most important treatment for patients with solid tumors, targeted therapy now plays an increasingly important role in this respect. The first such example is apparent in breast cancer, where expression of the oncogene HER-2 can be detected in 20–25% of cases, while the expression of HER-2 correlates with poor disease-free survival and resistance to chemotherapy and endocrine therapy. An antibody known as trastuzumab (Herceptin), and a humanized mouse anti-HER-2 monoclonal antibody, were found to inhibit HER signaling and thereby inhibit disease progression and enhance survival (Figure 1.14). Today, Herceptin plus chemotherapy represents the best drug treatment for metastatic breast cancer.

Currently, many other anti-cancer antibodies are available for the therapy of diseases such as solid tumor, lymphoma, and leukemia (Table 1.2). It has been well established that sustained angiogenesis is crucial to cancer, and cancers can by themselves trigger the growth of new vessels by inducing the secretion of growth factors (e.g., vascular endothelial growth factor; VEGF). Moreover, the angiogenesis may support tumor growth and metastasis by supplying nutrition to the cancer cells. Anti-angiogenesis is therefore an evidence-based therapeutic strategy. Approaches to modulate VEGF or VEGF receptor signaling include the targeting of VEGF or its receptor with antibodies that reduce VEGF expression by using ribozymes and RNA interference (Figure 1.15). Anti-angiogenesis, as expected, may cause vessels to regress, and this would lead to tumor shrinkage. This anti-cancer strategy has now achieved some degree of clinical success in metastatic colorectal cancer, it being reported recently that the anti-VEGF antibody, bevacizumab, increased overall survival when co-administered with chemotherapy as compared with chemotherapy alone (Figure 1.16).

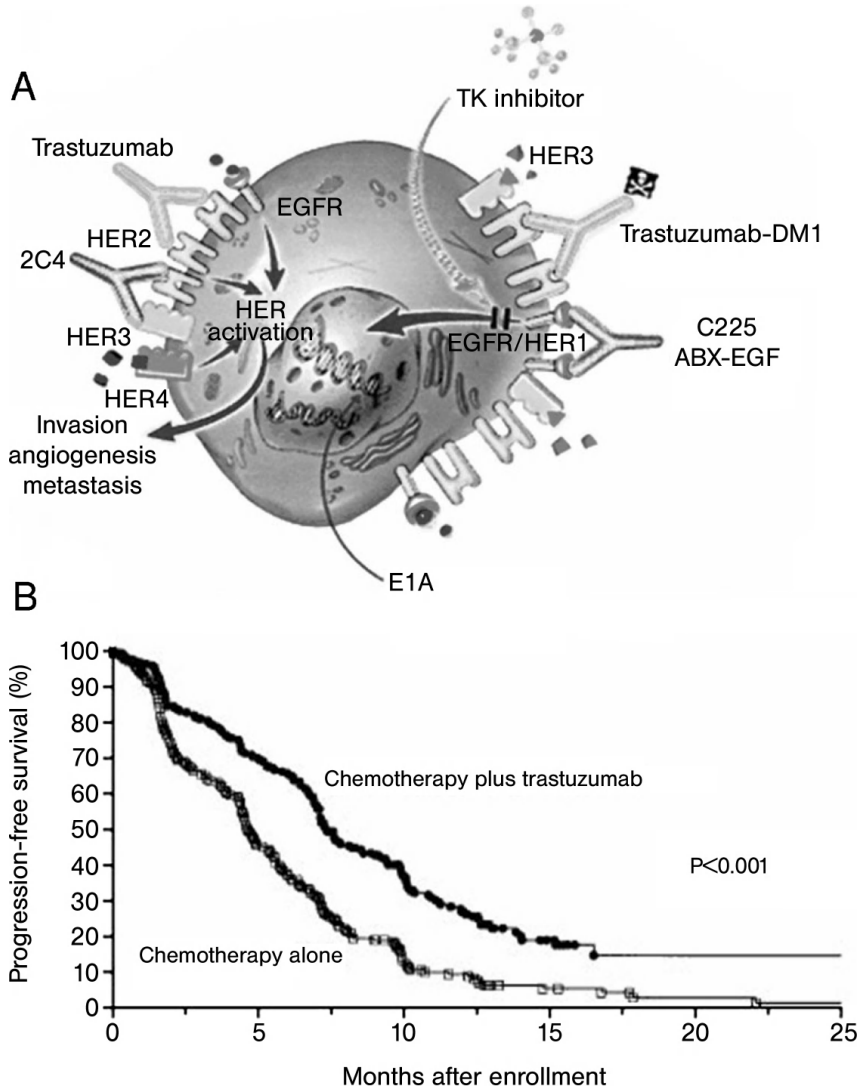


Figure 1.14 Trastuzumab as an example of an anticancer antibody therapeutic.

(A) Areas of potential therapeutic intervention.

(B) Trastuzumab combination therapy of breast cancer.

Table 1.2 Overview of FDA-approved targeted anticancer antibody therapeutics.
(Source: Ross et al., Am. J. Clin. Pathol. 122, 598–609, 2004).

Name	Date approved	Source (partners)	Type	Target	Approved indication	Diagnostic test required
Alemtuzumab (Campath)	May 2001	ILEX Oncology, San Antonio, TX; Schering, AG, Berlin, Germany	Monoclonal antibody, humanized; anticancer, immunologic; multiple sclerosis treatment; immunosuppressant	CD52	CLL	no
Rituximab (Rituxan)	November 1997	IDEC, La Jolla, CA (Genentech, South San Francisco, CA; Hoffmann-La Roche, Basel, Switzerland; Zenyaku Kogyo, Tokyo, Japan)	Monoclonal IgG1; chimeric; anticancer, immunologic; antiarthritic, immunologic; immunosuppressant	CD20	NHL	no
Trastuzumab (Herceptin)	September 1998	Genentech (Hoffmann-La Roche; ImmunoGen, Cambridge, MA)	Monoclonal IgG1 humanized; anticancer, immunologic	p185neu	Breast cancer	yes
Gemtuzumab (Mylotarg)	May 2000	Wyeth/AHP, Madison, NJ	Monoclonal IgG4 humanized	CD33/ calicheamicin	AML (patients > 60 y)	no
Ibritumomab (Zevalin)	February 2002	IDEC	Monoclonal IgG1 murine; anticancer	CD20 ^{90Y}	NHL	no
Edrecolomab (Panorex)	January 1995	GlaxoSmithKline, London, England	Monoclonal IgG2A murine; anticancer	EpCAM	Colorectal cancer	no
Tositumomab (Bexxar)	June 2003	Corixa, Seattle, W/A	Anti-CD20 murine monoclonal antibody with ¹³¹ I conjugation	CD20	NHL	no
Cetuximab (Erbix)	February 2004	Imclone, New York, NY; Bristol Myers, Princeton, NJ	Anti-EGFR	EGFR	CRC in combination with CPT-11 (irinotecan)	yes
Bevacizumab (Avastin)	February 2004	Genentech	Anti-VEGF (ligand)	VEGF	CRC; first line in combination with 5-FU	no

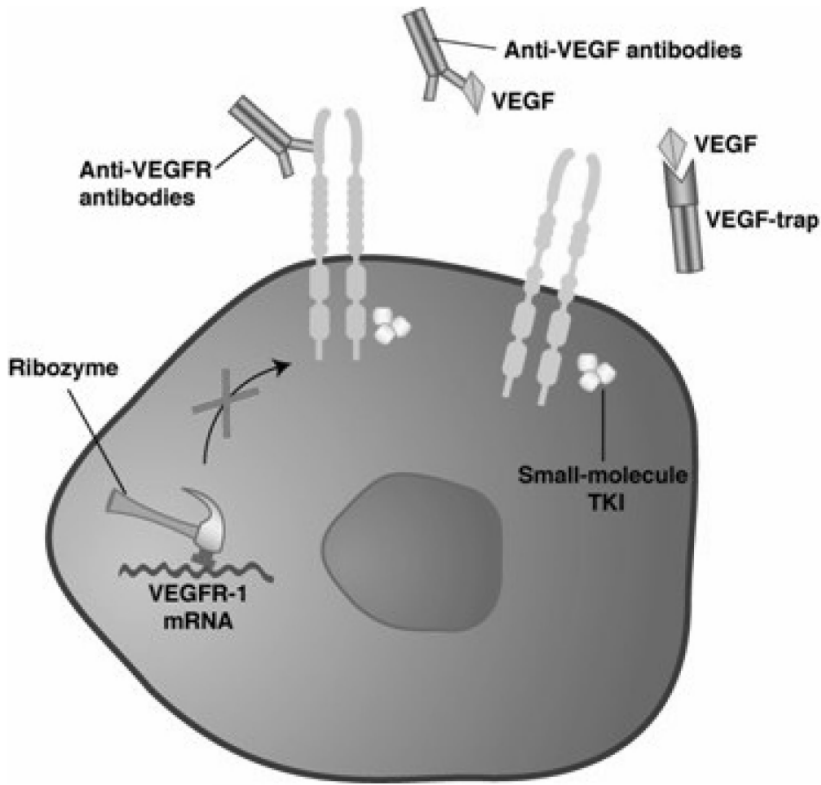


Figure 1.15 Approaches to modulate VEGF/VEGFR signaling.
(Source: Steward, *Horizons in Cancer Therapeutics* 5, 11–21, 2004).

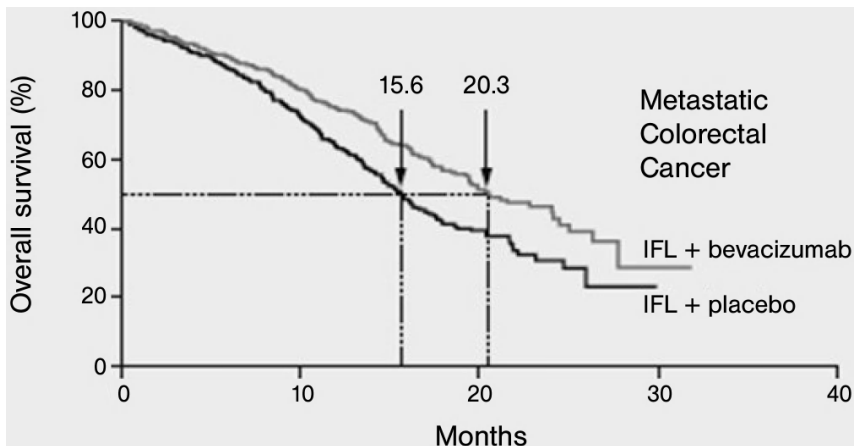


Figure 1.16 Bevacizumab: an anti-VEGF antibody in the combination therapy of colorectal cancer (IFL = irinotecan, fluorouracil, leucovorin).

1.4

Lung Cancer

The question of how the clinical outcome of lung cancer treatment might be further improved is urgent, notably because among cancer patients this condition is the number one killer worldwide, including China. Non-small-cell lung cancer (NSCLC) accounts for about 85% of all lung cancers, and a major advance during the past few years has been the use of a new small compound, gefitinib, in the treatment of this condition. Gefitinib treatment induces a marked remission of lung cancer in about 10% of patients in western countries and in 30% of cases in oriental countries, particularly in Japan and China (Figure 1.17).

The mode of action of gefitinib in the treatment of lung cancer is unclear, although inhibition of the mutant epidermal growth factor receptor (EGF receptor) is known to underlie gefitinib's anti-lung cancer activity. In contrast, gain-of-function mutations of the EGF receptor are critical to carcinogenesis of NSCLC. In ancient China, one of the main principles of combating disease was to treat a disease before its onset, and this might represent the advent of preventive medicine in oriental countries. The prevention of cancer from its onset, or of cancer progression, may be seen in many forms. For example, tobacco smoking can cause cancer of the lung and of other organs, as well as other respiratory and/or cardiovascular conditions, but when the patient stops smoking the improvements are remarkable. Typically, in a study of 14.5 years' duration, the mortality rate due to lung cancer was much lower in sustained "quitters" of smoking than in those who quit intermittently or who continued to smoke (Figure 1.18).

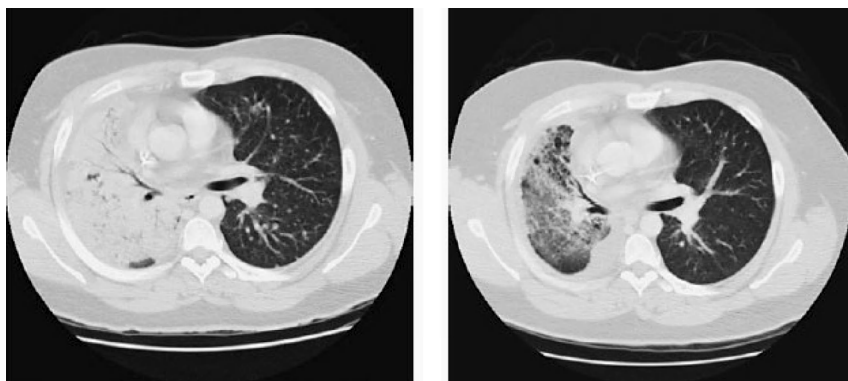


Figure 1.17 Gefitinib in the therapy for non-small cell lung cancer. Tomographic scans of a patient with lung cancer before (left) and 6 weeks after treatment with gefitinib (right). (Source: Lynch et al., *N. Engl. J. Med.* 350, 2129–2139, 2004).

1.5

Outlook

In China, the widespread use of hepatitis B vaccination dramatically reduced the virus infection ratio, and consequently the number of patients suffering from liver cancer has decreased by 25% over the past 15 years. It can be concluded, therefore, that a skillful doctor cures illness when there is no sign of disease, and thus the disease never materializes – as was proposed in China by Dr. Huai Nan Zi, some 2100 years ago.

The main steps for cancer prevention, though not easy to maintain, are clear – to stop smoking and to avoid alcohol over-indulgence, to eat a healthy diet, and to protect the body against sunlight, X-rays, chemicals, industrial agents and viruses. In addition, it is advisable to maintain a healthy body-weight, to stay active, and to undergo routine cancer screening. Knowledge concerning certain medicines that might prevent cancer, for example green tea, might also be beneficial.

In conclusion, cancer represents a group of heterogeneous malignancies and genetic abnormalities that underlie the elusive process of carcinogenesis. At present, molecular target-based therapies show great promise and, when combined with conventional procedures, may indeed represent the future of cancer treatment. Thomas Edison once said, “I am long on ideas, but short on time, I expect to live only 100 years”. Of course, everybody – including

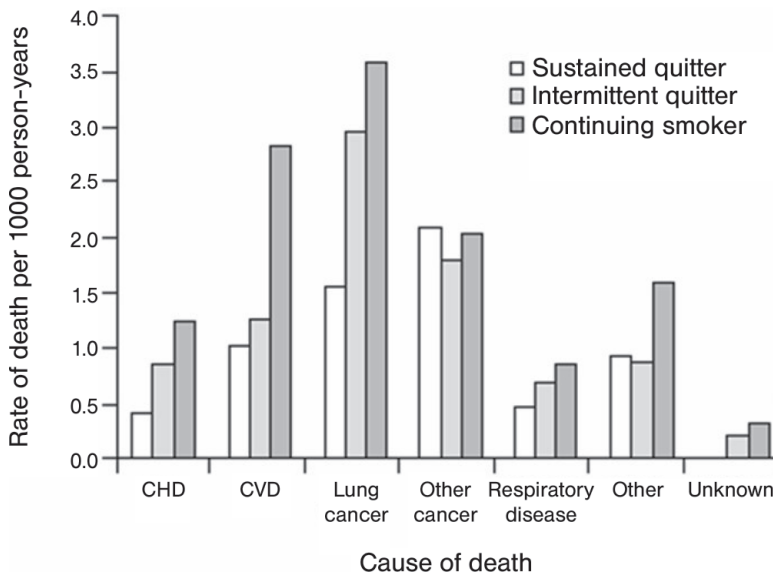


Figure 1.18 Influence of smoking habits on lung cancer. CHD = coronary heart disease; CVD = cardiovascular disease.

those suffering from cancer – wishes to live longer, and winning the war against cancer forms the focal point for those investigating the therapy and research of the condition. However, this cannot be achieved without the support of the general public, of the patients, of the pharmaceutical industry, of the decision makers, and of society in general.

Author Biography

Ciro A. de Quadros



Director, International Programs, Sabin Vaccine Institute (US)

Ciro de Quadros, M.D., M.P.H., has dedicated his career to freeing the world of infectious diseases, especially those that disproportionately affect the health and social development of the world's poorer countries.

At present he is the Director for International Programs at the Sabin Vaccine Institute (SVI), since February 2003. Before joining the SVI he was Director of the Division of Vaccines and Immunization of the Pan American Health Organization in Washington, D.C.

He completed his medical studies in Brazil in 1966 and received a Master of Public Health degree from the National School of Public Health in Rio de Janeiro in 1968. He was involved with the pioneering experiences for the development of the strategies of surveillance and containment for Smallpox eradication and in February, 1970 joined the World Health Organization (WHO) as Chief Epidemiologist for the Smallpox Eradication Program in Ethiopia. He transferred to the Pan American Health Organization (PAHO) in February 1997 to serve as the Senior Advisor on Immunizations. While working at PAHO he directed the successful efforts of polio and measles eradication from the Western Hemisphere. He retired from PAHO in 2002 and since 2003 has led Albert B. Sabin Vaccine Institute's international programs, with emphasis in advocacy activities directed at the control and/or elimination of rotavirus and rubella in Latin America and the Caribbean. He is also the chairperson of the Independent Review Committee of the Global Alliance for Vaccines and Immunization (GAVI) and serves on the Board of the International Aids Vaccine Initiative (IAVI). He is on faculty at the Johns Hopkins Bloomberg School of Hygiene and Public Health and the Schools of Medicine at Case Western Reserve University, in Cleveland and the George Washington University, in Washington, DC. He has published over 120 scientific papers and book chapters in peer

reviewed journals and has lectured in over 200 scientific meetings and conferences throughout the world. Ciro A. de Quadros has received several international awards, including the 1993 Prince Mahidol Award of Thailand, the 2000 Albert B. Sabin Gold Medal, the Order of Rio Branco from his native Brazil, and most recently, was named International Health Hero by the School of Public Health of the University of California at Berkeley. In 2004 he was elected Member of the Institute of Medicine of the National Academies of the United States of America.

2

Eradication of Vaccine-Preventable Diseases: Is it Possible and Cost-Beneficial?

Ciro A. de Quadros

2.1

Introduction

With regard to the question of whether investments in new therapies are paying off, there is perhaps no better example than the role of vaccines and their power in controlling diseases. Previously, much has been written about vaccines being the most effective health intervention system currently available, and this chapter will focus on some aspects and examples of disease eradication through vaccine use. This will include examples of successes and failures and aspects regarding the organization of eradication programs, followed by a brief description of the cost-effect and cost-benefit of the eradication of poliomyelitis and measles in the western hemisphere. The chapter will conclude with some possible insights into the future of disease eradication, and outline some of the lessons that have been learned so far.

2.2

Disease Eradication

By definition, disease eradication is the absence of a disease agent in nature in a defined geographical area, whereafter control measures can be discontinued once the risk of importation is no longer present. Whether control measures are interrupted or not, a disease can still be eradicated. Such a concept is permanently evolving in terms of eradication, and this can be seen from the definitions proposed at a meeting held at Dahlem near Berlin, Germany, several years ago, when “eradication” was defined in terms of different levels of disease control (Table 2.1, upper portion). On the first level, the disease is reduced to acceptable levels, and then proceeds to a level defined as “elimination”. Continuing, there is the elimination of infection in a defined

Table 2.1 Levels of control of vaccine preventable diseases.

Dahlem definitions (1997):

- Control = reduction to acceptable levels
- Elimination (of disease or infection) = no new cases in defined areas; control measures are maintained
- Eradication = worldwide absence of new infections; control measures can be discontinued
- Extinction = infectious agent no longer exists in nature and laboratory

Post-Dahlem (Decatur) definitions:

- Control = reduction to acceptable levels
- Eradication = no new infections in defined areas; control measures can be discontinued if there is no risk of reintroduction
- Extinction = infectious agent no longer exists in nature and laboratory

area, again with continued measures, until eradication and finally elimination at the global level is reached. At this point, the measures may be discontinued. The final stage is extinction of the disease, which refers to the elimination of an infectious agent, both in nature and in the laboratory. These definitions have been the subject of much debate, since many of the terminologies translate differently in different languages. Thus, a smaller group met in Decatur, Georgia, to define control as simply three levels: (1) a reduction to acceptable levels; (2) eradication in a defined area, which might be regional, worldwide and control measures which could be discontinued if no risk of introduction existed; and (3) extinction, both in nature and in the laboratory (Table 2.1, lower portion).

2.2.1

Criteria of Disease Eradication

In order to eradicate a disease it is necessary to fulfill certain criteria which are basically biological and/or societal. In this respect, humans must be essential to the life cycle of an infectious agent, and there is a specific intervention to interrupt transmission of the infectious agent from one person to another. In practice, diagnostic instruments are available that will be sufficiently sensitive and specific to detect transmission of the infectious agent. Finally, there is a societal interest in the eradication of a disease, and this of course is related to the disease burden – how the disease is seen by society and the cost to eradicate it.

Among previous eradication initiatives, perhaps the most well-known (and first) viral disease to be eradicated was smallpox. Edward Jenner had declared more than 200 years ago that the use of his vaccine would extinguish smallpox

Table 2.2 Past eradication initiatives.

<i>Year</i>	<i>Initiator</i>	<i>Disease</i>	<i>Region</i>	<i>Outcome</i>
1801	Jenner	Smallpox	Global	Failed
1911	Gorgas	Yellow fever	The Americas	Failed
1915	Rockefeller Commission	Yellow fever	Global	Failed
1950	Soper	Smallpox	The Americas	Failed
1955	WHO	Malaria	Global	Failed
1958	Zhdanov	Smallpox	Global	Succeeded
1985	PAHO	Polio	The Americas	Succeeded
1988	WHO	Polio	Global	Uncertain
1994	PAHO	Measles	The Americas	Succeeded
2003	PAHO	Rubella	The Americas	Uncertain

from the face of the earth (Table 2.2). In 1904, King Charles III of Spain sent an expedition to the Spanish colonies in America and the east in an attempt to stop the transmission of smallpox. In 1911, Gorgas attempted to eradicate yellow fever in the Americas, and this was followed by the Rockefeller Commission's attempt to globally eradicate this disease. In 1950, the Pan-American Health Organization (PAHO) launched an effort to eradicate smallpox in the Americas. The World Health Organization (WHO) attempted to eradicate yaws on a regional basis, and also tried to eradicate malaria globally. In 1958, Professor Zhdanov from the then Soviet Union proposed the eradication of smallpox, whereafter PAHO in 1985 proposed the eradication of polio in the Americas. In 1986, the WHO started a program for Guinea worm eradication in most parts of Africa, while in 1988, following the success of the eradication of polio in the Americas, the WHO launched a polio eradication scheme on a global level. In 1994, when the Americas were certified polio-free, the PAHO launched an effort to eradicate measles and in 2003, when the transmission of measles had been interrupted in the Americas, the directing council of the PAHO again launched a program to eradicate rubella from the Americas.

However, most of those initiatives, including yellow fever and malaria, failed because they did not fulfill the biological criteria for eradication. In fact, to date only the global effort to eradicate smallpox has succeeded, though it is hoped that polio eradication will in time also be successful. Measles eradication has been successful in the Americas, but this has not quite been the case for rubella, although progress to date has been outstanding. However, it is believed that during the next two to three years, rubella transmission will be interrupted in the region of the Americas.

2.3

Launching Eradication Programs

The next question is how and when to launch eradication programs. Clearly, it is essential to examine the reality of science – the biological versus the hope factor – since the result can be fatal if these aspects are not considered. An example of this is the failure of malaria eradication, which almost led to the breakdown of the WHO.

One very important factor is the duration of the program, and in this respect epidemiological models allow committed partners to share the financial responsibilities. The tension that exists from a horizontal approach versus a vertical approach must also be recognized. This debate has raged for more than a century, since it relates to the importance of the strategy that will be applied to the eradication program. Certain other factors that will influence the coverage of a program must also be considered, including the technicians involved, the feasibility of the study, and the adaptation and issue of human resources, which is critical. The perception of the problem by politicians, the trust of the community, and sometimes even the coercion of the community (as occurred in many regions of the world during the smallpox eradication program), and finally the commitment of funding, costs and economics involved, will all impact upon the duration of the program. Put simply, an eradication program cannot continue for ever – it must have only a limited (usually very limited) lifetime.

A number of external factors must also be considered, some of which are positive and some negative. The former category includes a guarantee of the common principles that create mutual benefits, in particular the use of eradication programs to reinforce health systems and infrastructure in different countries. An important example of this was poliomyelitis in the Americas, since the program was launched not only to eradicate polio but also to reinforce the infrastructure of health systems, and particularly the surveillance and logistical systems.

Negative aspects include a suboptimal implementation that may lead to resistance, thereby increasing the long-term problem, and economic difficulties such as the development of human resources, the laboratory network that can be created (and has been created with polio eradication and measles eradication in the Americas), and the political capital for public health. In developing countries, the weakest minister is usually the one holding the health portfolio, and conquering or re-controlling disease will increase the political capital of that sector. These negative aspects may become dangerous practices if left uncared for, and increased costs may lead to the termination of coordinated schemes.

2.4

Examples of Disease Eradication

The two main examples of eradication from the Americas are those of polio and measles.

2.4.1

Polio

The strategy used initially for polio – and now utilized worldwide – was the routine immunization of children by the health services, coupled with supplemental immunization combined with national immunization days and mopping-up operations with surveillance of acute flaccid paralysis. This approach was first implemented in Cuba, when Albert Sabin first developed the oral polio vaccine and showed that national immunization days could stop transmission; indeed, Cuba was the first country to stop the transmission of polio in 1962. As a result, this approach was implemented in all countries in the Americas, such that the disease disappeared (Figure 2.1). The last indigenous case of polio occurred in 1991 in Peru, and in 1994 the region was declared polio-free. In 2000, there was a resurgence in the Hispaniola Island, with an outbreak provoked by a reversion of the vaccine virus.

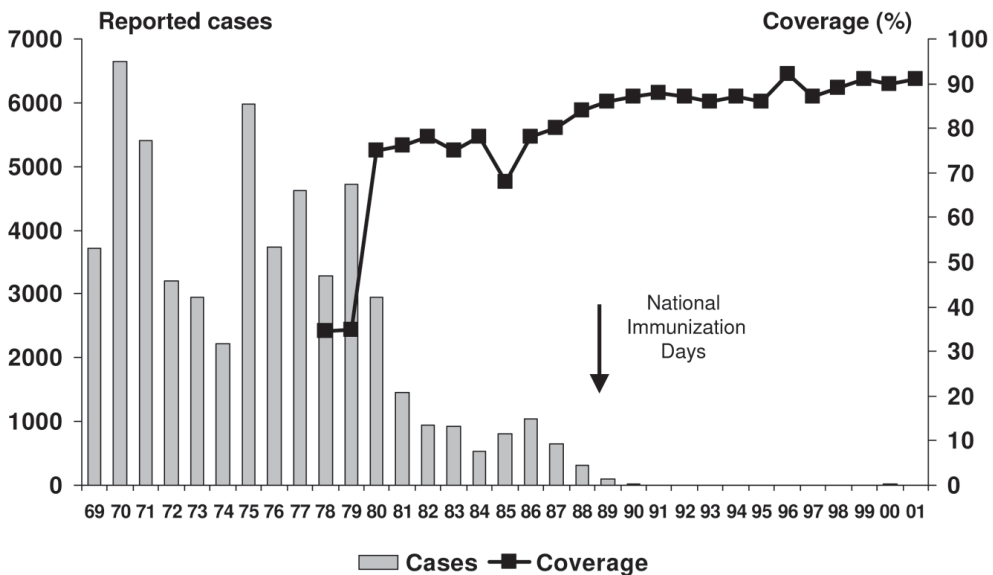


Figure 2.1 OPV3 vaccination coverage and incidence of paralytic poliomyelitis in the Americas. Coverage is for children aged over 1 year. Data for 2000 and 2001 represent Type 1 vaccine derived virus. (Source: HVP/PAHO).

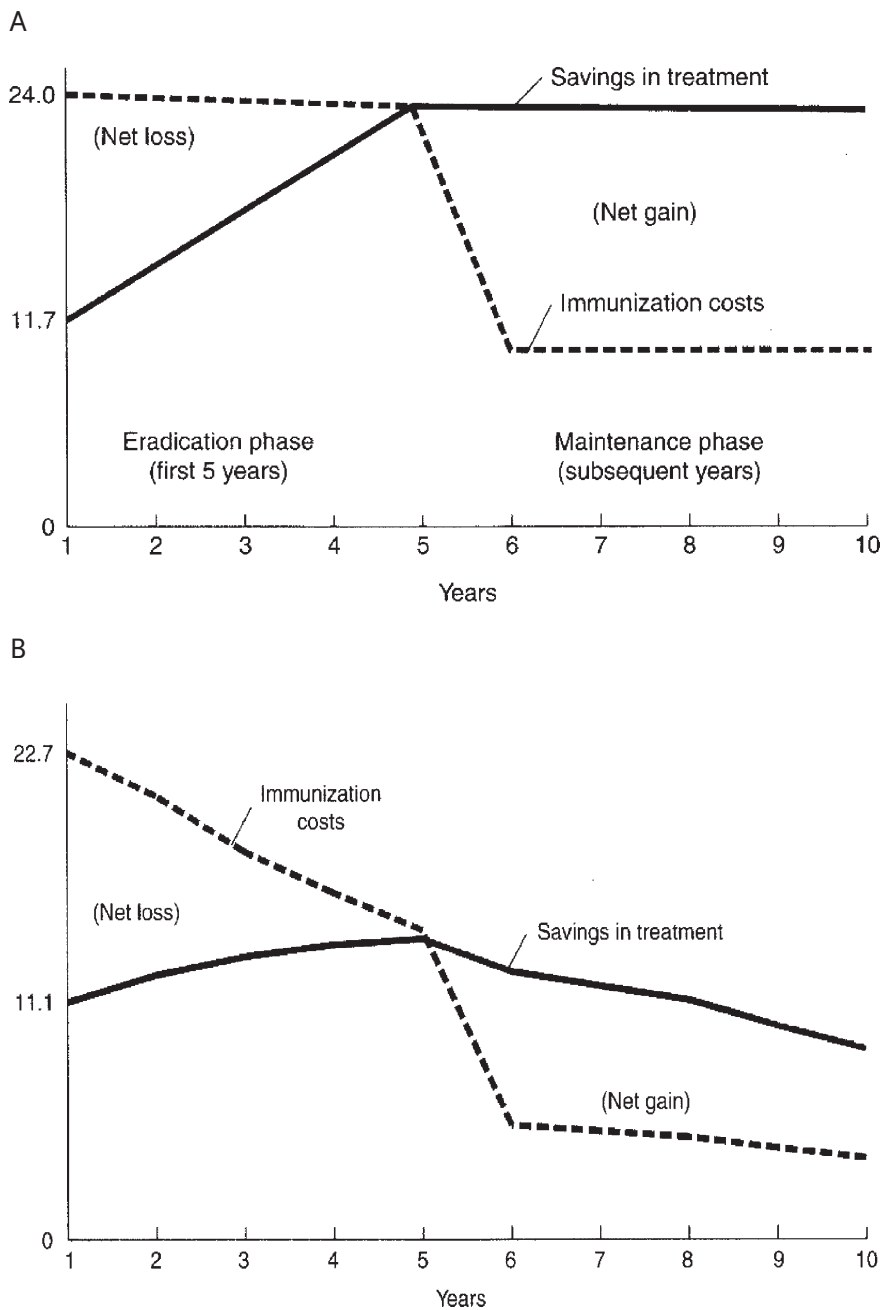


Figure 2.2 Costs and benefits of polio eradication.

(A) No discounting. (B) 12% discounting per year.

The study assumes treatment of only some victims.

(Source: P. Musgrove, *Health Economics and Development*, World Bank, 2003).

Table 2.3 Costs and benefits associated with polio eradication during a successful five-year campaign and an ensuing 10-year maintenance period. (Source: P. Musgrove, Health Economics and Development, World Bank, 2003).

Total costs versus benefits (figures are US\$ million, except where indicated)	Treatment of all victims		Treatment of only a portion of the victims	
	First 5 years	All 15 years	First 5 years	All 15 years
No. of cases prevented ('000)	70	220	15	55
Savings in treatment expenses	408.0	1282.4	87.5	320.7
Cost of eradication or maintenance	120.0	220.0	120.0	220.0
Net savings (net benefit)	288.0	1062.4	-32.5	100.7
Net present value of discounted savings	217.2	481.4	-27.3	18.1

The costs and benefits associated with polio eradication during the successful five-year campaign and an ensuing ten-year maintenance period are listed in Table 2.3 and illustrated graphically in Figure 2.2. The net present value of discounted savings was US\$ 480 million for the period under study, and even if all cases had not been treated (as was likely in many developing countries and Latin America), the net present value of discounted savings was still in the order of US\$ 18 million.

The ultimate justification for a US\$ 2 billion polio eradication scheme is that the children involved would grow up to be healthy, and would be productive members of society, and thereby contribute to the GMP of their country. Clearly, consideration must be given to human lives and suffering rather than simply to the dollars involved.

2.4.2

Measles

The measles elimination strategy in the Americas relied on the catch-up campaign – that is, the vaccination of all children aged between 1 and 14 years with one dose of measles vaccine during the low season, the aim being to interrupt transmission. This was followed up by vaccination during routine services (termed the “keep-up”), and a very high coverage was achieved in children aged 12 to 23 months in order to maintain an interruption of transmission. Obviously, this is possible if the health systems can be reinforced so that they deliver vaccines on a daily basis. It is important that the maximum coverage possible is achieved throughout the country, and here again vaccines may represent one of the most equitable health interventions, simply because they can reach every child, as has been shown in several efforts worldwide.

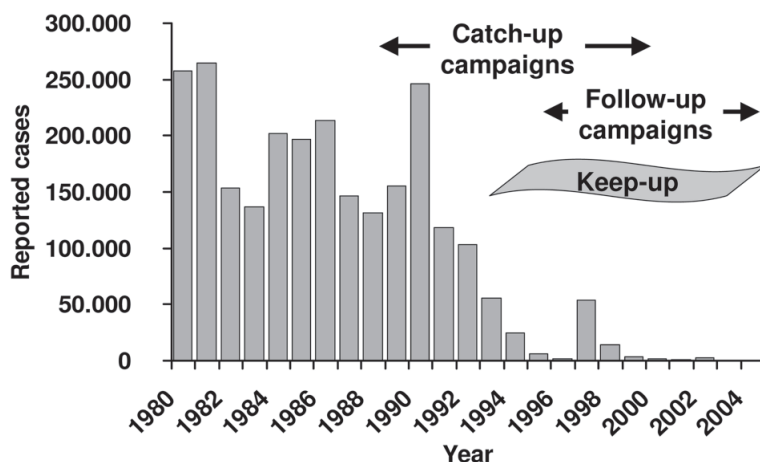


Figure 2.3 Measles cases in the Americas, 1980–2004.

Periodic mass campaigns, termed “follow-up” campaigns, are conducted every four years, and are aimed at vaccinating children aged 1 to 4 years. The goal would be to provide the first dose to those children who missed their first dose during the routine service. This approach is now referred to by WHO and UNICEF as a second opportunity for the child to obtain their first dose of vaccine, though of course the majority will receive a bonus second dose, thereby maintaining an interrupted transmission. Figure 2.3 shows, graphically, the impact of catch-up campaigns on measles cases in the region. The campaigns were again started in Cuba, followed by the English-Caribbean and other countries, such that over a period of about 8–10 years, all of these countries had implemented campaigns and improved their routine services, after which periodic follow-up campaigns were implemented.

2.5

The Costs of Immunization

A breakdown of the components of routine immunization programs is illustrated in Figure 2.4. The highest expenses are related to administrative costs and vaccine delivery. When examining the aggregate cost of measles elimination in Latin America, the savings over a 21-year period were on the order of US\$ 200 million (Table 2.4). Again, the dollar figures were high, but more important is the fact that over the past few years, no child has died of measles in Latin America, or in the whole of the western hemisphere.

Sadly, in Japan about two or three years ago, over 50 children died from measles. It is unacceptable that in today’s world, where vaccines cost so very

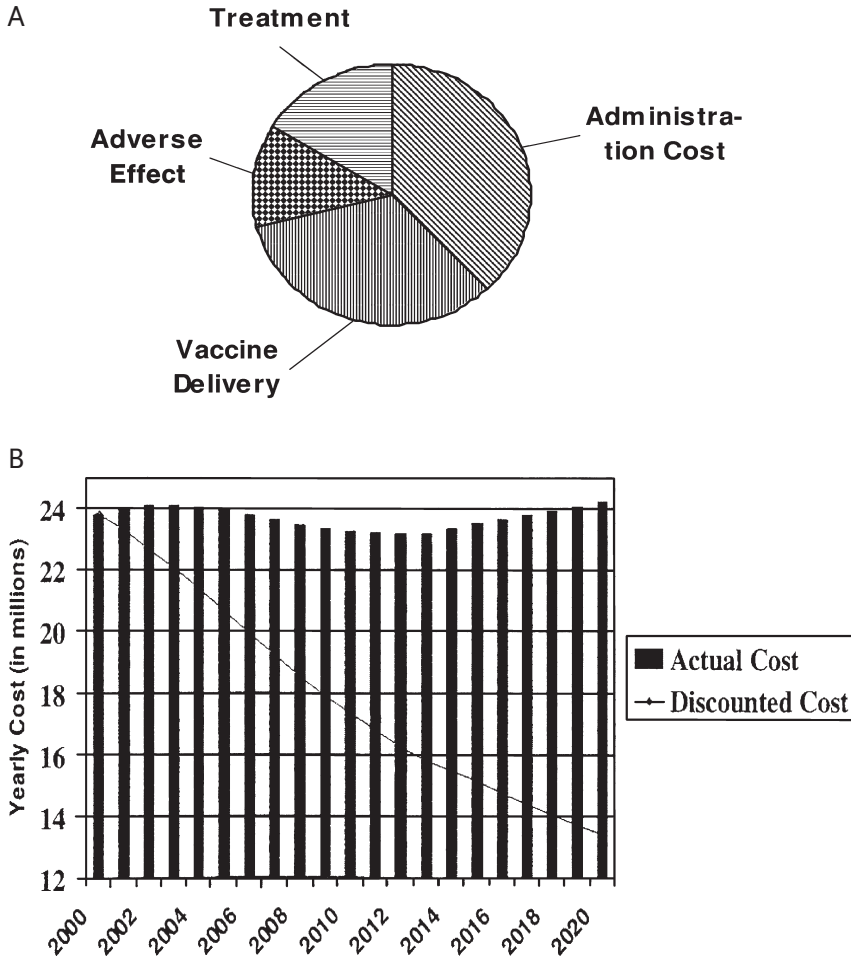


Figure 2.4 Cost of measles eradication program in the Americas.

(A) Component breakdown of yearly costs for 2000.

(B) Estimated yearly costs for 2000–2020.

(Source: Acharya et al., *Vaccine* 20, 3332–3341, 2002).

little, children are still allowed to be paralyzed by polio, to die from measles, or be born with malformations due to congenital rubella. Society must change this social “norm”.

On the other hand, the cost of failure and the loss of trust in public health programs can be enormous. Consequently, extreme care must be taken when the decision is taken to eradicate a disease. There is also a loss of opportunities to introduce new vaccines, as well as biological issues related to pressure in the selection of vectors, or resistance to parasites that will increase the cost of control in the future.

Table 2.4 Aggregate cost of measles elimination in Latin American countries. All costs in the lower half of the table are discounted at 3% and extrapolated to entire Latin America. (Source: Acharya et al., Vaccine 20, 3332–3341, 2002).

Description	Cost (US\$ million, 1999)
Cost of routine program	
• Year 2000	23.8
• Years 2000–2020 (discounted at 3%)	376.4
Cost of follow-up program	
• Year 2000	38.4
• Years 2000–2020	172.0
Cost of the entire program	
• Years 2000–2020	548.4
• Extrapolated to entire Latin America	571.2
Cost of measles program without elimination effort	779.5
Cost savings due to the elimination program	
• Years 2000–2020	208.3

In this respect, political commitment is critical, and strategies must be clearly understood at all levels of the health system, as well as by those involved in the implementation. Clearly, it is not possible to have a rigid strategy, and research data must be available that fit into the program, so that a strategy can be adapted as it progresses. The resources must also be adequate and easily available. For example, when the program was launched in the Americas, the resources were not easily obtained, and indeed a chronic problem of global polio eradication is that the resources are always in short measure. There must also be strong management, research facilities to guide the strategy, adequate international coordination, a motivated staff, and a time limit for the completion of the program.

2.6
Future Prospects

When considering future prospects for the eradication of viral diseases, a number of approaches have been made in the past, and clearly more will be made in the future. Some of the diseases listed in Table 2.5 are not eradicable, some form the basis of a major disease burden worldwide, and in societal terms some are not even on the politicians’ “radar screens”. However, if polio can be eradicated, then measles may well be the next target for eradication.

Table 2.5 Prospects for the eradication of viral diseases.

<i>Disease</i>	<i>Eradication feasible?</i>	<i>Eradication likely?</i>
Yellow fever	no	–
Rabies	no	–
Juvenile encephalitis	no	–
Influenza	no	–
Varicella	no	–
Hepatitis A	yes	no
Hepatitis B	yes	no
Mumps	yes	no
Rubella	yes	yes
Measles	yes	yes

Likewise, rubella eradication is succeeding in Latin America and in the western hemisphere, and in March 2005 it was declared as being “interrupted” in the United States.

2.7 Summary

In conclusion, it is important to understand the natural history of a disease before launching a program for its eradication. There must be extensive consultation before program initiation, and surveillance must be carried out from the start of the program in order to provide the strategy with guidance. The approach also requires a vertical tactic which, if well applied, may be very helpful for improving health systems. Moreover, it is necessary to expect the unexpected, so there must be flexibility. Of course some countries will require more assistance than others, and this situation must be well analyzed, the costs considered, and the funding readily available. In this respect, the coordination of partners is essential, and victory must not be declared too soon. It was Louis Pasteur who stated that, “... it is within the power of man to eradicate infection from the earth”, and there is no other health intervention more powerful than vaccines.

Author Biography

Peter B. Corr



Senior Vice President, Science and Technology, Pfizer

Dr. Peter B. Corr is Senior Vice President for Science and Technology at Pfizer Inc., where he is responsible for aligning the company's worldwide research and development organization with licensing activities, science and medical advocacy, global medical relations and science policy.

He has had a long and distinguished career in science and technology, including positions in both academia and industry. Prior to joining Pfizer in 2000, he held senior leadership positions in research, development and discovery at both Warner-Lambert Company and Monsanto/Searle.

Peter B. Corr, who received his PhD from Georgetown University School of Medicine and Dentistry, spent more than 18 years as a leading researcher in molecular biology and pharmacology at Washington University. His research, published in more than 160 scientific manuscripts, has focused on the biochemical mechanisms, with particular emphasis on ischemic heart disease, sudden cardiac death and other abnormal cardiac rhythms.

He is the recipient of numerous awards, including Alpha Omega Alpha National Medical Honorary Society, an Established Investigator Award from the American Heart Association, and a Research Career Development Award from the NIH. In 1981, he received the Washington University School of Medicine Teacher of the Year Award, and in 1980 the Washington University Distinguished Faculty Award.

He has also served on or is serving on the editorial board of several journals, including *American Journal of Physiology*, *Circulation*, *Circulation Research*, *Molecular and Cellular Biochemistry*, and the *Journal of Cardiovascular Electrophysiology*.

3

Incentives in Policy Reforms Necessary to Stimulate Activity

Peter B. Corr

3.1

Introduction

In my contribution I would like to emphasize both the challenge and opportunity to make clear improvements in the difficult health problems that we are facing today, both in the developed and developing worlds. It is possible that we are victims of our own success, as science has become such a massively complex body of knowledge that no one person, discipline, institution or company can manage it in its entirety. The technological demands and complexity of today's research methods are not only "mind-boggling", they are also very expensive to conduct. At the same time, from a policy perspective, the array of regulations that medicines face as they spread across the globe creates another set of challenges. Medicines are the most regulated entity in the world, and indeed it is only right that they should be. They must show both efficacy and safety. To maintain this requires a concerted effort to be made by all concerned, but we also have to think about how we balance the risks and benefits.

3.2

High Attrition: High Costs

Today, one of the key challenges faced by the pharmaceutical industry is that of high failure rates and attrition in research and development as, taken together, these rapidly drive up costs. In general, a basic research finding – that is, a particular target or targets – leads to the development, via biological and chemical routes, of a particular molecule that will interact specifically with that target (Figure 3.1). Subsequently, a single compound is selected and moved into preclinical development, where it undergoes very expensive testing

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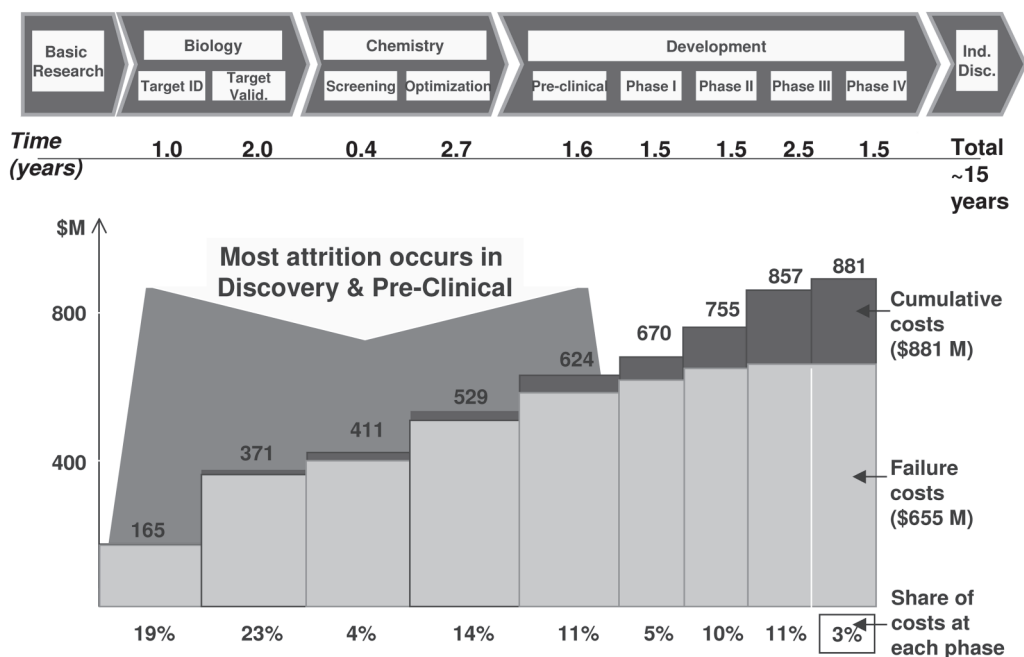


Figure 3.1 High attrition contributes to high R&D costs.

in areas of toxicology and pharmacokinetics. Finally, the molecule is moved into man where, with good fortune, the new drug passes through various stages of clinical development and then to regulatory approval. The overall duration of this process varies from drug to drug, but typically ranges from 10 to 15 years.

Why is this process so expensive? The analysis shown in Figure 3.1, which was conducted by examining data from several companies, suggests that a figure of US\$ 880 million is reasonable. However, by examining the share of cost at each phase, it is clear that the main problem is that of failure costs which, in the case illustrated, is US\$ 655 million on average. Of course, if in some way success could be identified at the start of the process, this would reduce costs by some 75%. Attrition is very high during the preclinical phase. In consequence, millions of compounds are screened by the pharmaceutical companies each year, yet very few reach the marketplace.

The world as a whole seems to believe that much more is known about the biology of disease than is true. In this respect the learning process is continuous, and much valuable information is obtained from the failures. The result is that, despite these enormous challenges, there is great optimism within the pharmaceutical industry that the cusp of a new paradigm is rapidly approaching.



Figure 3.2 The three “A”s of the biomedical industry.

3.3

Availability, Accessibility, Affordability

At Pfizer, the commitment is to making medicines available, accessible, and affordable – what is known as the three “As”. Although effective, this strategy and commitment requires both good science and good business (Figure 3.2):

- First, medicines must be made *available* – that is, they must be discovered, developed, manufactured and distributed.
- Second, they must be made *accessible*, physicians and patients must be taught about them, and they must be dispatched where and when they are needed, worldwide. Accessibility has other connotations, however, in terms of infrastructure, delivery systems, and health professionals working across sectors to connect the patient to the therapy, and this represents a major problem in the developing world.
- Finally, medicines must be made *affordable*. The challenge is to ensure that third-parties pay for medicines when appropriate, and to provide help for those people who cannot pay for them by their own means when necessary, and to price according to the markets in which they are accessible.

This entire system rests on the foundation of the availability of new medicines. Availability is a matter of science and large investment.

Today, more than ever, there are three indispensable elements that help make these medicines available, accessible and affordable:

- The unique abilities of the biomedical industry to discover, test and develop new therapies on a sufficiently large scale, and with efficiencies sufficient to meet the global burden of disease are essential.
- The involvement of the public sector is essential to maximize the efforts of the biomedical community by advancing basic science in both the private and public sectors. It is also necessary to identify how better regulatory

strategies and efficiencies can be provided, to support a sound intellectual property system, and to use such a system to provide incentives in the right way. It is also important to balance the need with a careful understanding of what is scientifically possible.

- There must be stronger partnerships across all sectors, in order to prevent duplication and to maximize efficiencies. Partnerships represent the real goal, as the complexities, risks and high costs of R&D demand that members of the biomedical community coordinate their efforts. Much more can be accomplished, with much less redundancy, if institutions and organizations work together and bring their combined strengths to bear.

3.4

Innovation and Partnership

In the spirit of partnership, what is needed to fuel innovation and to realize the promise of biomedical endeavor? Although tens of billions of dollars are being spent, the opportunity remains largely unrealized. The requirements are clear. First and foremost is a successful healthcare system that provides an efficient delivery and distribution of services, together with efficient pricing and reimbursement for these services. Healthcare systems must be sustained by the effective use of intellectual property, including the enforcement of intellectual property rights, such that investment in discovery, basic science and development will continue. There should also be prevention of parallel trade, so that patients in developing countries will have access to affordable medicines, usually at zero or near-zero cost. Healthcare systems must be supported by adequate and predictable regulatory requirements, including a safe and efficient drug approval process and, importantly, a global harmonization of regulatory requirements. This may well be the key to success, as a great deal of money is spent performing different studies for different regions of the world. A rapid adjustment of regulatory requirements to current advances in science and technology is also requisite.

How do we know these elements are so critical to innovation? Because the record proves it. During the past 20 years, the pharmaceutical and biotechnology industries have brought to patients well over 90% of all new medicines developed worldwide. In fact, today there are 700 new therapies in development alone, all at high risk to the companies and at very high cost. It is also known that innovative medicines have the capacity to reduce morbidity and to lessen the need for expensive hospital care. As an example, treatment with inexpensive cholesterol-lowering drugs can reduce the need for subsequent expensive angioplasty procedures and coronary artery bypass graft surgery. Over the past 40 years, the use of medicines has helped to reduce numbers of

hospital admissions by half for 12 major diseases, including ulcers, mental illness and infections. Moreover, it is known that investments in R&D contribute to economic competitiveness, and that more competitive medicines can consistently reduce the cost burden of disease, particularly if patients are diagnosed earlier, treated earlier, and compliance to treatment is markedly improved compared to the present situation. This latter point applies not only to the developed world but also to some extent to the developing world.

3.5

The Economic Value of Health

In a study conducted by Kevin Murphy and Robert Topel, two economists at the University of Chicago, an analysis of US data showed that even modest reductions in death rates due to common killers such as cancer, heart disease, diabetes, pneumonia and influenza could produce literally trillions of dollars in added economic benefit to society via these affected individuals over their lifetime. For example, a 10% reduction in deaths from diabetes – bearing in mind the rapid worldwide increase in diabetes – would provide US\$ 450 billion in overall economic benefits to society during the lifetime of America's present living population (Table 3.1). Moreover, this situation can be extrapolated throughout the world.

Table 3.1 The economic value of health.

<i>Cause of death</i>	<i>Impact of 10% decrease (US\$ billion)</i>
Major cardiovascular diseases	5142
Malignant neoplasms	4359
Infectious diseases (including AIDS)	644
Chronic obstructive pulmonary diseases	605
Pneumonia and influenza	358
Diabetes	449
Chronic liver disease and cirrhosis	310
Accidents and adverse effects	1369
Homicide and legal intervention	413
Suicide	508
Other	3006
All causes	17163

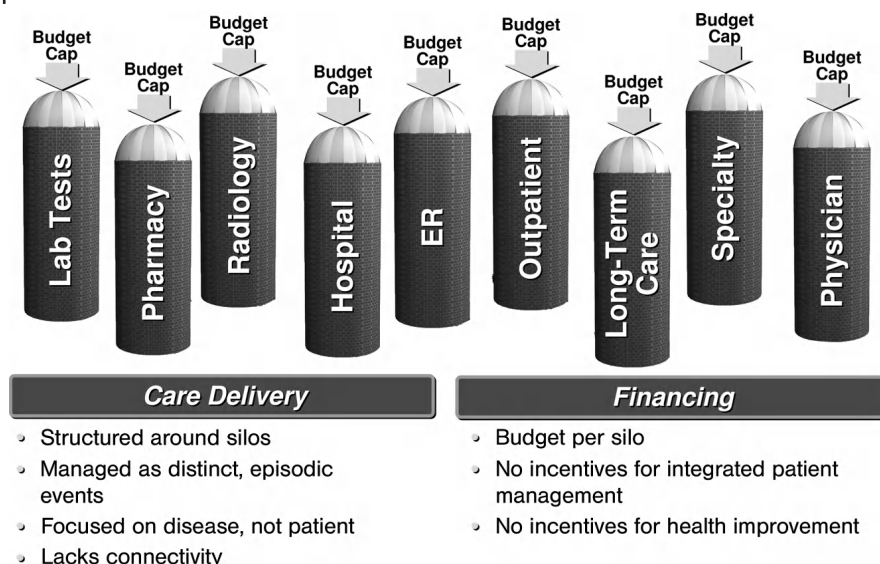


Figure 3.3 The current healthcare management and delivery paradigm.

These examples of economic benefit are exactly why healthcare regulators and governments should focus on the cost burden of disease than simply on the cost of therapies to treat that disease. Unfortunately, the problem in Europe and the US – and to some extent in Japan and other countries in the developed world – is that the approach towards healthcare resembles a series of many unconnected “silos” (Figure 3.3). Whether it is the hospital, the physician, the pharmacy, or even the insurer, each silo only considers ways to reduce costs within its own sphere of influence. Yet if healthcare is considered in its entirety, from preventive measures to early diagnosis and treatment, it is possible to see where strategic investments could reduce the cost burden of disease for society as a whole, in terms of care delivery and financing. By treating these required therapies as a cause to be managed rather than as a long-term investment in the health of society, governments in Europe and elsewhere have enacted policies that undermine health.

The healthcare system in the US has also had its share of problems. The system is under extreme pressure, but it is not coincidence that only five of the world’s current 20 top-selling medicines were discovered by companies based in Europe and Japan, where governments maintain tight controls on spending for new medicines and thereby inadvertently undermine an active science base in a free market. The other 15 medicines of the top 20 have emerged from America. There are indeed many problems in the US, but the market there is more receptive and the climate is better for biomedical investment and research. Consequently, Europe’s economic competitiveness

may well be determined by its ability to innovate. The EU research commissioner recently stated, in January 2005, that "... overall progress in increasing Europe's research investment is far too slow as member state investment targets are too often put aside, policy measures do not go far enough or they are not pursued".

3.5.1

Aging and Longevity

The situation in Europe is especially relevant with regard to medical challenges and costs related to aging and longevity. In the year 2050, it is predicted that four of every 10 people in Italy and Japan will be aged over 60 years, and that some European countries will have more citizens aged over 80 than under 20 (Figure 3.4). The convergence of rising longevity and declining fertility carries enormous economic and social implications, including more medicines, more hospitalizations, and an increased demand for healthcare. These pressures will not be sustainable in future decades unless the challenges and opportunities of aging are met in a dramatically different way. The key to this is the formation of new partnerships, and an important part of a new approach which links all components of healthcare. One such example is a partnership between the International Longevity Center and Pfizer. This non-profit organization conducts research and advises scholars and thought leaders on how to maintain well-being and productivity throughout life and into old



Figure 3.4 Predicted age distribution in European countries by the year 2050. Note that there are more citizens aged ≥ 80 years than aged ≤ 20 years.

age. At Pfizer, the phenomenon of aging is viewed as a major opportunity to rethink how societies view the entire range of health issues. In this regard, policy makers in the EU and national governments are being engaged to emphasize the link between health and overall economic benefits to society, by working together to build productive alliances and partnerships. By proving that economic benefit comes with early diagnosis and early treatment, the aim is to achieve shared goals. Currently, this spirit of partnership is also producing excellent results in the so-called neglected diseases of the developing world.

3.6

The “10–90 Gap”

It has been claimed that only 10% of global health research is devoted to conditions which account for 90% of the global disease burden: this is referred to as the “10–90 gap”. I would like to be a little provocative and argue that there is no 10–90 gap, and that in poor countries the problem is one of inadequate access and infrastructure to deliver currently available drugs. The fact is that private companies are responsible for discovering, developing and producing virtually all medicines currently on the World Health Organization essential drug list, and industry continues to discover and develop many effective and safe medicines that address significant health problems in the developing world. These range from infectious diseases such as HIV/AIDS, tuberculosis, malaria, or tropical parasitic illnesses to non-communicable conditions that are now emerging as a serious double burden for the populations of the developing world. Moreover, as the lifespan of the population in developing countries continues to increase, the non-communicable diseases of the developed world will become major scourges of disease within the developing world. One recent example was the discovery and development of novel products to combat malaria. At Pfizer, one such drug is currently undergoing Phase III clinical trials, whilst several other companies have established research centers focusing on tuberculosis and other infectious diseases. It is important that this approach is continued and conducted in partnership with governments, with nongovernmental organizations (NGOs), and in collaboration with other companies.

3.7

Incentives to Stimulate Innovation

There is a need to create incentives to speed the discovery and development of medicines, and to address existing gaps in developing countries (Figure 3.5).

- ▶ **Public-Private Partnerships**
- ▶ **Advanced Purchasing Commitments**
- ▶ **A Global Fund for Tropical Diseases**
- ▶ **Tropical Diseases Drug Act**

Figure 3.5 Incentives to stimulate innovation.

(Source: Addressing the Health Needs of the Poorest Populations: Lessons Learned and Remaining Challenges in the Fight Against Neglected Disease. International Federation of Pharmaceutical Manufacturers Association, October 2004).

Examples of these incentives include public–private partnerships that attract funding to finance applied research in areas that are currently unattended. Typical examples include the Global Alliance for TB, and the Medicines for Malaria venture, whilst others are developing a growing portfolio of agents against tropical diseases.

A second incentive is that of advanced purchasing commitments, which represents an attempt to correct an absence of sustainable funding mechanisms and an effective market in countries that are too poor to purchase any innovative drugs. These advanced purchasing commitments create the promise that new medicines will be purchased and that R&D efforts in tropical diseases will be worthwhile. In other words, a set price and volume provide the necessary reward for the R&D effort in lieu of a real market.

A global fund for tropical diseases should also be considered to ensure that purchasing funds are made available to countries and communities that need medicines. Moreover, these funds should be made available at very low cost. An example of this is the Global Fund against AIDS, tuberculosis, and malaria, a demand-driven model which comprises a consortium of public and private sector NGOs that develops and submits grant applications.

Finally, a Tropical Diseases Drug Act, similar to the Orphan Drug Act, could be introduced, although key to the success of this would be the introduction of partnerships. The biomedical industry with their experience in the “real world” could shape the role of these new partnerships. Business should provide the lion’s share of funding, and drive the emergence of a more efficient, more effective paradigm for biomedical research – a paradigm that should have a huge impact on the three A’s. By sharing resources and infrastructures, these partnerships would also limit the risk to all partners. Each new project could be responsive to a wider variety of needs and a richer array of insights and more institutions. As a result, organizations would have ownership over some part of the process, but more people would have a stake in its success.

3.8**Treatment or Prevention?**

Many people in the developed world will reach the age of 85 years, and by that time, based on current statistics, half of them will have Alzheimer's disease. At present, therapies exist to treat the symptoms, but not to alter the progression of the disease; an example of this is Aricept. The question is that, given the choice, should investment now be made in very difficult studies, with huge numbers of failures, in order to prevent progression of this disease? The alternative is to start building institutions that will house the millions of people aged 85 and who will have dementia. Clearly, the same choice applies to a whole range of diseases and, whilst there are no guarantees, it is likely that the incredible advances in biomedical research will provide effective treatments that will not only dramatically improve medical outcomes but also reduce the cost to society.

So, in response to the question posed in the title of this module, of whether investments in new therapies are paying off, the reply is undeniably, yes.

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Module II

Developing, Manufacturing and Using Vaccines: Which one is most Critical?

Introduction

Dominique Lecourt

Growth of biotechnologies for the production of new vaccines has occurred through several stages. From traditional vaccines (poliomyelitis, tetanus, tuberculosis, measles ...), we have advanced to more sophisticated ones such as that against hepatitis B or meningitis. Today, a whole pallet of new prophylactic and therapeutic vaccines are in various stages of development, including vaccines against malaria and cervical cancer caused by the papilloma virus. The genetic constitution of the viruses appears extremely promising. How can we make these vaccines, both old and new, accessible to the greatest number of people? Although initiatives such as the Global Alliance for Vaccines and Immunization (GAVI) are leading the way, their progress also points to the obstacles. Foremost among these are economic and political barriers due to the lack of medical infrastructure in many countries where millions of children could be saved by vaccines. The lack of financial resources is often as important as the lack of political will. Perhaps more alarming is the distrust of vaccination by the general public. It is urgent that politicians in developing countries regard vaccination as well as education as a priority. In order to reduce the inequalities between North and South, shouldn't one consider producing the necessary vaccines in the same countries where their lack is felt so acutely? The fact is that mortality rates resulting from pathogens to which vaccines are targeted are much higher in developing countries than in developed countries.

Author Biography

Sir Gustav Nossal



Professor Emeritus, Department of Pathology, University of Melbourne

Gustav Nossal was born in Bad Ischl, Austria, in 1931, and came to Australia with his family in 1939. He studied Medicine at The University of Sydney and, after residency at Royal Prince Alfred Hospital, took his PhD at The Walter and Eliza Hall Institute of Medical Research in Melbourne. Apart from two years as Assistant Professor of Genetics at Stanford University, one year at the Pasteur Institute in Paris, and one year as a Special Consultant to the World Health Organization, all Nossal's research career has been at the Hall Institute, of which he served as Director (1965–1996). Nossal was also Professor of Medical Biology at The University of Melbourne.

Nossal's research is in fundamental immunology, and he has written five books and 530 scientific articles in this and related fields. He has been President (1986–1989) of the 30,000-member world body of immunology, the International Union of Immunological Societies; President of the Australian Academy of Science (1994–1998); a member of the Prime Minister's Science, Engineering and Innovation Council (1989–1998); and Chairman of the Victorian Health Promotion Foundation (1987–1996). He has been Chairman of the committee overseeing the World Health Organization's Vaccines and Biologicals Program (1993–2002) and Chairman of the Strategic Advisory Council of the Bill and Melinda Gates Children's Vaccine Program (1998–2003).

4

Developing Affordable Vaccines

Gustav Nossal

4.1

Introduction

Before highlighting the rich promise of biotechnology in the development of new and improved – and, above all, affordable – vaccines, the question should perhaps first be asked, what is a vaccine? The essential prerequisites for a vaccine are straightforward (Figure 4.1). From a technical standpoint there must be vaccine molecules, termed antigens, and these are frequently present on the surface of a pathogen. There must also be a “danger” signal to alert the immune system that something is afoot. Then, there must be three healthy sets of cells collaborating with one another in order to set the immunological cascade in motion. The scavenger cells (technically known as dendritic cells) must be present to take up the antigen, become activated, and in turn activate a cell known as a T lymphocyte. The latter cell has a dual function: first, it attacks infected cells; and second, it helps the antibody-forming cells, the B lymphocytes, rapidly to synthesize specific antibodies.

Essential Pre-requisites for a Vaccine

- ▶ Vaccine molecules (antigens), frequently from the surface of a pathogen.
- ▶ A “danger” signal to alert the immune system.
- ▶ Three healthy sets of cells collaborating with one another:
 - dendritic or scavenger cells to take up antigen;
 - T lymphocytes to attack infected cells;
 - B lymphocytes to make specific antibodies.

Figure 4.1 Essential prerequisites for a vaccine.

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4.2

The “Danger” Signals

With regard to the nature of these danger signals, it appears that an ancient, evolutionary system of receptors on scavenger cells (among others) was designed to recognize pathogen-associated molecular patterns. This is probably the prime example of a danger signal. In addition, proteins can be released from dying cells following viral infection or tissue damage as a result of inflammation, and this generates the immune response. In the laboratory, the danger signals are artificially created by preparing chemical mixtures, termed adjuvants, that may contain several such activators. Harmless attenuated viruses may themselves signal danger and may be genetically engineered to produce several antigens.

4.3

Bioengineered Vaccines

Several well-known examples of bioengineered vaccines have been prepared through modern biotechnology (Figure 4.2). One such example is the hepatitis B surface antigen (HBsAg), which is currently prepared in yeast cells. These molecules self-aggregate and self-assemble into virus-like particles that are attracted towards scavenger cells, thereby achieving major vaccination success against a very serious pathogen.

In a more complex scenario, involving GlaxoSmithKline (GSK) and the US Department of Defense, the malarial antigen from the surface of the parasite as it leaves the mosquito (the so-called circumsporozoite protein) is fused to the HBsAg. In this way, a virus-like particle is formed that can be mixed with strong adjuvants such as RTS or S-ASO2. After almost two decades of

Interesting Examples of Bioengineered Vaccines

- ▶ Hepatitis B surface antigen (HBsAg) made by yeast cells.
- ▶ The malarial antigen from the surface of the parasite as it comes out of the mosquito (CSP) fused to HBsAg to form virus-like particles, mixed with strong adjuvant chemicals.
- ▶ The polysaccharide-protein conjugate vaccines against meningitis (such as Hib and Mening C).

Figure 4.2 Examples of bioengineered vaccines.

problematic research, good partial protection is now available in African children, and the proof of principle that the malaria community so ardently desired has clearly been provided.

The polysaccharide–protein conjugate vaccines represent an intelligent option as they utilize T-cell/B-cell collaboration. In the initial step, the B cells recognize the contact-specific polysaccharide, which is then conjugated to a protein. This appears to “annoy” the helper T cells, and results in a much better response than if the polysaccharide alone were present. The first such vaccine to be introduced in practice was *Haemophilus influenza* B, and this proved highly successful against meningitis. A vaccine against *Streptococcus pneumoniae* has only recently been developed. The results of a huge, four-year study involving 17 000 young children in The Gambia, West Africa were published in *The Lancet* (25th March, 2005). The nine-valent vaccine was seen to be 77% effective in preventing pneumococcus-derived pneumonia. Moreover, it reduced the incidence of pneumonia from all causes by 37%, and reduced all-cause mortality by 16%. In other words, a vaccine directed against acute respiratory disease is saving children’s lives incontrovertibly, and with very high statistical significance.

4.4

Biotechnological “Tricks” in Vaccine Production

Most widely used, currently available vaccines have been developed on the basis of good antibody production. After all, this is the target of the researcher in preclinical studies, and is what happens in experimental animals. Although antibodies are produced by B cells, some infections must be combated by T cells attacking the infected cells and secreting protective molecules associated with the inflammatory process. Two key examples of this are tuberculosis and HIV/AIDS. One problem with this is that the sustained activation of cytotoxic T cells has been difficult to achieve, especially in subhuman primates and humans. Thus, a number of biotechnological “tricks” have been developed (but not yet perfected) to promote T-cell activation. The first is to use viruses that have been genetically engineered to ferry pathogen antigens into the body; this is the “Trojan horse” concept (Figure 4.3).

The original virus used widely in experimental animals is vaccinia (the smallpox virus) and its variants, which are double-stranded DNA viruses. Adenoviruses (also double-stranded DNA viruses) have been widely used, as have variants of the AIDS virus itself, which are retroviruses and of course single-stranded RNA viruses. In addition to using the Trojan horse to carry in the antigenic pathogen, it is also possible to co-express with the antigen certain stimulatory molecules, termed cytokines. This makes the immune response stronger, and even naked DNA encoding antigens can be used. In fact, some

Some Biotechnology Tricks Promoting T Cell Activation

- ▶ Use of viruses genetically engineered to ferry pathogen antigens into the body (the Trojan horse concept).
 - Vaccinia and variants (DS-DNA)
 - Adenoviruses (DS-DNA)
 - Retroviruses (SS-RNA)
 - Co-expression of cytokines
- ▶ Use of “naked” DNA encoding antigens; some formulations include a scavenger cell targeting strategy.
- ▶ “Prime-boost” strategies:
 - DNA prime – protein boost
 - DNA prime – viral boost

Figure 4.3 Biotechnology tricks promoting T-cell activation.

recent formulations of DNA vaccines have included a scavenger cell targeting strategy, where the antigen of molecules for which the scavenger cells have receptors is attached to the DNA.

The problem is that this does not achieve a strong and consistently long-lasting cytotoxic T-cell response. Consequently, it was decided to focus the response on the T cell by using a “prime-boost” strategy – that is, DNA priming with either a protein boost or viral boost. This approach, although attractive, is currently only at the experimental animal stage or in very early Phase I clinical trials, and is far from complete.

4.5

Needle-free Immunization

4.5.1

Mucosal Immunization

The concept of needle-free immunization has been under consideration for some time, with mucosal immunization being a major contender. In laboratory animals, vaccines can function effectively when introduced via mucosal surfaces, including oral, intra-nasal, respiratory, and rectal surfaces. The problem in this situation is that as well as the antigen of interest, a strong mucosal adjuvant is also required; typical examples include the B subunit of cholera toxin, mutants of the *Escherichia coli* heat-labile toxin or camptothecin (CPT) conjugate oligonucleotides. If such a mucosal adjuvant is available, it can be covalently coupled to the antigen, thereby reducing the quantity of

antigen required, which is a very practical point. Unfortunately, although the mucosal immunization strategy shows great promise, very few supportive clinical data are currently available.

4.5.2

Transdermal Immunization

Transdermal immunization represents an alternative form of needle-free immunization. The dendritic cells lie quite superficially in the skin, and model antigens are able to penetrate the skin, especially if it has been heavily pre-moistened. Again, an adjuvant is required for immunogenicity, and the development of such materials has led to considerable interest among smaller biotechnology companies. The main interest is in formulations which allow better penetration of proteins into the skin. As an alternative, some companies are producing very fine, almost brush-like, needle-like arrays in patches. These can be glued onto the skin, avoiding needle pricks, but are still at the experimental stage.

4.6

Genome Mining

Genome mining represents a new concept of antigen development. Today, the entire genome sequence of many pathogens, viruses, bacteria and parasites is available. These data can be analyzed using bioinformatic software to identify genes which code for surface-exposed proteins, virulence factors, molecules involved in cell invasion, or other vaccine candidate proteins. Moreover, by using recombinant DNA technology, the relevant proteins can be easily synthesized and individually tested in mice. As an example of this reverse vaccinology, Chiron has tested 350 proteins of *Neisseria meningitidis* group B. Although as yet there is no freely available vaccine against meningitidis B, 28 novel antigens have been identified which elicited bactericidal activity in mice. Currently, the Chiron group is patiently working through these antigens, hoping to develop a vaccine “cocktail” that is effective in humans.

4.7

Vaccine Affordability

Two examples spring to mind of how the world is addressing the problem of vaccine affordability. The first of these relates to rotavirus, which was discovered by Ruth Bishop and Ian Holmes in Australia some 30 years ago, and is the most powerful viral cause of diarrhea among infants. In fact,

rotavirus kills some 600 000 infants each year. Recently, in January 2005, GSK launched its oral live attenuated single strain G1 Rotarix vaccine in Mexico. Although not hot news, this was the first occasion that a multinational corporation had gone to a developing country where the problem lay, had used that country's regulator to obtain the first registration, and negotiated with that country to introduce the vaccine into the population. Jean Stephenne will discuss this vaccine in more detail in Chapter 6. GSK has announced that there will be three levels of tiered pricing for this vaccine: a high price if it is eventually introduced into wealthy countries; a medium price for countries in transition (e.g., Mexico); and a low price for those countries that are the poorest of the poor.

In this respect, GSK is not alone, with Merck having studied more than 70 000 infants in 11 countries after administration of their oral, three-dose human-bovine reassortant vaccine containing five strains, the so-called RotaTeq. The vaccine was 74% effective against any diarrhea, impressively (98%) effective against severe diarrhea, and was also well tolerated.

There is an emerging research capability in the developing world itself, with India and Indonesia both having interesting rotavirus vaccine candidates. However, these are not as far advanced along the research pipeline as the vaccines, which are already in use. Particular interest has been expressed in the Indonesian version (this is Ruth Bishop's original strain), although as yet the clinical efficacy has not been monitored.

4.7.1

The *Neisseria meningitidis* Serogroup-A Conjugate Vaccine

In the case of African meningitis, the *Neisseria meningitidis* serogroup-A conjugate vaccine represents a completely different answer to the affordability conundrum. It is well known that, every three to four years, vicious epidemics of meningitis sweep across the African meningitis belt from Senegal to Ethiopia, threatening 300 million people. The cause usually (but not always) is meningococcus A, and a US\$ 17 million grant from the Gates Foundation has proposed, for competition, the idea of a new monovalent group A meningitis vaccine. The best tender came from the Serum Institute of India in Pune, which has guaranteed to supply the vaccine at US 40 cents per dose. There is an interesting strategy in operation here, as the polysaccharide antigen and carrier tetanus toxoid will each be provided by manufacturers from an industrialized country, whereas the conjugation technology utilized will be transferred through an elaborate contracted collaborative venture. This major experiment is the responsibility of Marc LaForce, the eminent Canadian scientist leading the WHO Gates Foundation team. If it is successful, the low labor costs and great energy of developing country manufacturers can be used in the search for new and improved vaccines.

4.8

The Next Challenge

The next major challenge to the biotechnology of vaccinology is, most likely, that of more combination treatments and fewer needle injections (Figure 4.4). There is a need to combat the fact that, in many developing countries, disposable syringes are reused and so can transmit blood-borne diseases. Consequently, the introduction of auto-disable and uniject syringes is critical. Moreover, there is a need for vaccines that do not require refrigeration, or that would function earlier in life. An example of this is the famous “gap” in measles, where maternal immunity wanes at 4–6 months, but the available vaccine cannot be administered before the child is aged 9 months. It has been argued that unless a so-called “stealth” vaccine can be produced, which will “creep” under the residual antibody but still be able to protect 4-month-old children, measles might never be eradicated from the world. In Chapter 2, Ciro de Quadros suggested that, although this situation is not necessarily true if a highly disciplined approach is followed, vaccines which functioned earlier in life would be of great value. Clearly, the “holy grail” is vaccines for the big three diseases – HIV/AIDS, tuberculosis, and malaria – but these are still some distance away.

Other Biotechnology Challenges in Vaccinology

- ▶ More combinations, fewer needle-pricks.
- ▶ Autodisposable and uniject syringes.
- ▶ Vaccines which do not require a cold chain.
- ▶ Vaccines which function earlier in life (e. g. measles).
- ▶ Vaccines for the big 3 – HIV/AIDS, tuberculosis, malaria.

Figure 4.4 Biotechnological challenges in vaccinology.

4.9

Conclusion

To conclude on a note of hope, it would be nice to think that 2005 – the 50th anniversary of the discovery of the Salk vaccine – will be a historic turning point in how the question of producing vaccines for the developing world is approached. I would remind you of the comment made by the Irish poet Nobel laureate Seamus Heaney, when he heard that Nelson Mandela had at long last been released from jail: “A further shore is reachable from here. Once in a lifetime justice can rise up and hope and history rhyme”.

Author Biography

Jacques-François Martin



Member of the Board, GAVI, President, Global Fund for Children's Vaccines

Jacques-François Martin has spent the essence of his career in the pharmaceutical, biological and life sciences industries.

From 1970 to 1976, he was the Chief Executive Officer of *Rhône-Poulenc Pharma* in Hamburg, Germany. He then returned to France to join the *Institut Mérieux* as Vice President of sales and marketing, where he largely contributed to the international expansion of Mérieux. He was named the company's Chief Executive Officer in 1988, and successfully negotiated with the government of Canada to acquire *Connaught Laboratories*.

In 1991, J.-F. Martin set up *Parteurop S.A.*, a biotech consulting company based in Lyon, France. At Parteurop, as Chairman and CEO, he helps establish start-up companies by leveraging innovation from French and foreign institutions.

From 1996 to 1998, he was the Chief Executive Officer of the *Fondation Jean Dausset – Centre d'Etudes du Polymorphisme Humain*, a private foundation dedicated to genomics research.

From September 1996 to September 1999, he was a member of the Board of *INSERM* (Institut National de la Santé et de la Recherche Médicale, the French National Institute of Health).

From 1994 to 1997, he served as the Chairman of the *Biologicals Committee of the International Federation of Pharmaceutical Manufacturers Associations*. As such, he was a member of the Scientific Advisory Group of Experts of WHO (SAGE).

From November 1997 to June 2003 he was a member of the Board of the International AIDS Vaccine Initiative (IAVI).

From 2000 to January 2005, J.-F. held the position of President of *The Vaccine Fund*. He led the Fund's efforts to provide lifesaving vaccines and other

immunization program support to low-income countries. In this capacity, he was also a member of the Board of *GAVI* (Global Alliance for Vaccines and Immunization).

He is member of the Board of several life sciences companies.

J.-F. Martin holds a Master's in Business Administration from the Ecole des Hautes Etudes Commerciales.

5

Why “Affordable” Vaccines are Not Available to the Poorest Countries

Jacques-François Martin

5.1

Introduction

Today, work is progressing on many new vaccines, the need for which is unquestioned. There is, however, a paradox. At a meeting in Hanoi which centered on diseases (notably diarrheal) of the most impoverished nations, much concern was expressed that following the tsunami on 26th December 2004, enteric diseases prevalent in some of the affected countries might be dispersed, leading to serious epidemics. This was particularly the case for typhoid fever and cholera. The question was also asked that if these diseases are endemic in the countries referred to, and good vaccines are available to prevent cholera and typhoid fever, then why are we not using them?

We live in a strange world when it comes to vaccines. We are dreaming of new vaccines that are not yet available, whilst those that are available are not used appropriately. It was this reflection which led to the idea of renovating and revamping efforts to immunize children through the Global Alliance for Vaccines and Immunization (GAVI), which was started five years ago.

When this idea was first conceived, the situation was that among each annual birth cohort of about 130 million children, 36 million had no access to immunization. As a consequence, between two and three million children would die from a disease which could have been prevented by existing vaccines. If calculated on a monthly basis, three million per year approximates, in terms of death, a tsunami every month. In total, 250 000 children were dying – some say unnecessarily, I would say scandalously – from diseases which could be relatively easily prevented.

Why has this happened? Is it too difficult to develop the required immunization strategies? That is definitely not the case. We are all aware of the fantastic efforts deployed during the 1980s, when coverage in terms of immunization was very poor, through the early 1990s when, under the extraordinary

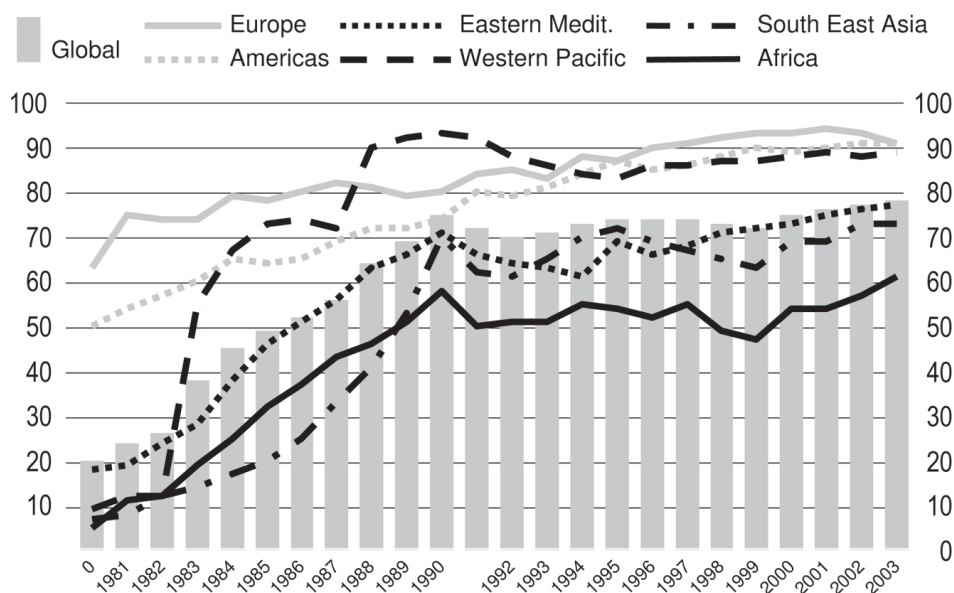


Figure 5.1 DTP3 coverage (in %), 1980–2003. (Source: WHO/UNICEF).

leadership of UNICEF and particularly, Jim Grant, substantial progress was achieved (Figure 5.1). During this period, whilst initially 10–20% of children were immunized with six basic vaccines, this figure ultimately rose to 60–80%, depending on the continent. Subsequently, and for a variety of reasons, the effort has not been sustained in a way to maintain, let alone improve these results.

In a nutshell, we have a track record of success with immunization, and we know how to do it. Still immunization is not performed appropriately. Is that because it is not cost efficient and we should have other priorities in healthcare? When comparing different health activities, in terms of lives saved per million dollars invested, immunization is among the most cost efficient (Table 5.1).

Table 5.1 Cost efficiency of immunization versus other health services for children. (Source: WHO, 2003).

<i>Intervention</i>	<i>Lives saved per million US\$ spent</i>
Enhanced program of vaccination (six standard antigens)	1500–2500
Control of malaria (different measures)	1200–1500
Treatment of cancer	2–10
Preventing HIV mother-to-child transmission	2500–5000

So, there is a medical need, the know-how is available, there is a track record of success, and the return on investment is among the best, why do these problems still exist? Several reasons have been suggested, but I will focus on three main elements, namely political commitment, access to vaccines, and the financial resources available.

5.2

Political Commitment

Immunization is an activity which must be sustained and systematized, because children are born continuously. Generally, immunization is carried out at the discretion of health clinics worldwide; it is not a spectacular activity and therefore requires constant political commitment to ensure that it is conducted as it should be. In many countries, health budgets are inadequate, without even considering development levels. For example, the African Union has suggested that African countries should spend 15% of their national budget on health in general. At present, this figure is, on average, 5%, so there is still room for progress. In both less-developed and developed countries, the notion of prevention is less popular than that of treatment, although it is much cheaper and much more efficient to prevent than to treat. Likewise, immunization does not sell well to politicians, because it is much more “spectacular” to open a new hospital than to support a continuous immunization activity. Overall, it appears that there is insufficient political commitment in many countries, and this was the situation some five years ago.

With regard to international organizations, institutions such as UNICEF and WHO have many different activities to develop in many fields, and so cannot be expected to have full-level priorities for all cases. For UNICEF, immunization has always been a major program, although the level of priority has changed with time. It is important to ensure that the appropriate organization maintains the momentum for immunization.

In the case of donations, the situation has arisen where donors expressed concern about how their money would be used, and what results would be achieved. A somewhat sterile debate was also continued on the benefits of a program approach versus a horizontal approach. Clearly, each health activity must be examined in the context of the broader health sector, as no one clinic worldwide performs only immunization. It is also clear that when children are immunized, access to many other health schemes is secured. The lack of political commitment in immunization is the reason why the GAVI was started five years ago – to motivate and coordinate activities between different players at national and international levels, to advocate the cause, to mobilize resources and, generally speaking, to reposition immunization as a centerpiece in the design and assessment of international development efforts.

5.2.1
The Results to Date

In terms of results achieved to date, the delivery of vaccine doses has clearly risen (Figure 5.2). We are particularly proud of the progress of hepatitis B (Hib) vaccine, which was launched in wealthy countries about 20 years ago, but has been used appropriately in developing countries only during the past five years. Today, this vaccine has been introduced into most developing countries, and basic vaccines such as DPT (diphtheria, pertussis, tetanus) have been improved. By contrast, the results with Hib are still probably insufficient; at the end of 2003, six million more children were reached with basic vaccines, and four to five million were reached with new vaccines, which is a clear breakthrough. The WHO has estimated that 700 000 deaths have been prevented by the additional immunization of these children. So, the initial number of 36 million children who remain un-immunized has, five years later, been reduced to about 27 million. Whilst this represents substantial progress, it shows that there is still much to do and that future efforts should be maintained.

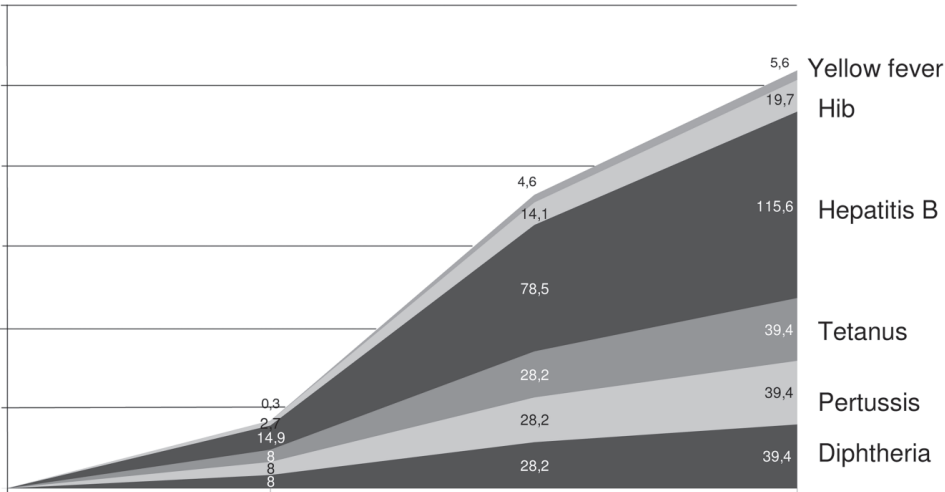


Figure 5.2 Delivery of vaccine doses by GAVI, in million doses, 2000–2003.

5.3

Access

Access to vaccination remains a major issue, and relates mainly to material points in terms of infrastructure. In particular, this applies to the cold chain (i.e., refrigeration), which is very often insufficient or old-fashioned and requires renovation. Many countries also have problems with transportation, though these apply to healthcare in general and not only to immunization. It is also important to know that progress is being made to reach inaccessible children, and not only those who are easily accessible. It appears that more effort is needed to develop outreach services when children have neither the possibility nor opportunity to visit health services. In this respect, the point must be made that in addition to its intrinsic value, immunization provides an excellent means of improving child access to many other health services. When the decision is made to fully immunize a child, it is imperative that the child attends the health service five times during the first year of life, as five injections must be given. If, in any country, 90% of newborn children are reached each year (this is the target for 2010), the indication is that there is in place the basic skeleton of a system that can be built on in order to improve access to other activities. This very proposal was the subject of a recent WHO review that dealt with the distribution of bed nets to protect against malaria at a time when children received immunization against measles.

One important part of the success of these programs is related to the issues of management and monitoring; these are very often neglected, leading in turn to substantial losses in terms of the efficiency of a country's health programs. It is also relevant at this point to mention the subject of insufficient human resources.

5.3.1

Health Worker Availability

When examining health worker density data by continent, there is seen to be wide diversity that is, perhaps, not unexpected (Figure 5.3). In wealthy countries, or where there is a tradition of global health, the average is almost 10 health workers per 1000 inhabitants. While ratios are already relatively low in Central and South America, the Middle East and Asia, the situation in sub-Saharan Africa is truly alarming, where there is less than one-tenth of the health workers present in more developed countries. On examining the potential consequences of this situation, there is seen to be a clear correlation between numbers of health workers per 1000 inhabitants and child mortality (Figure 5.4). Moreover, as long as there is no development in the health system of a country, the progress that can be made will be limited.

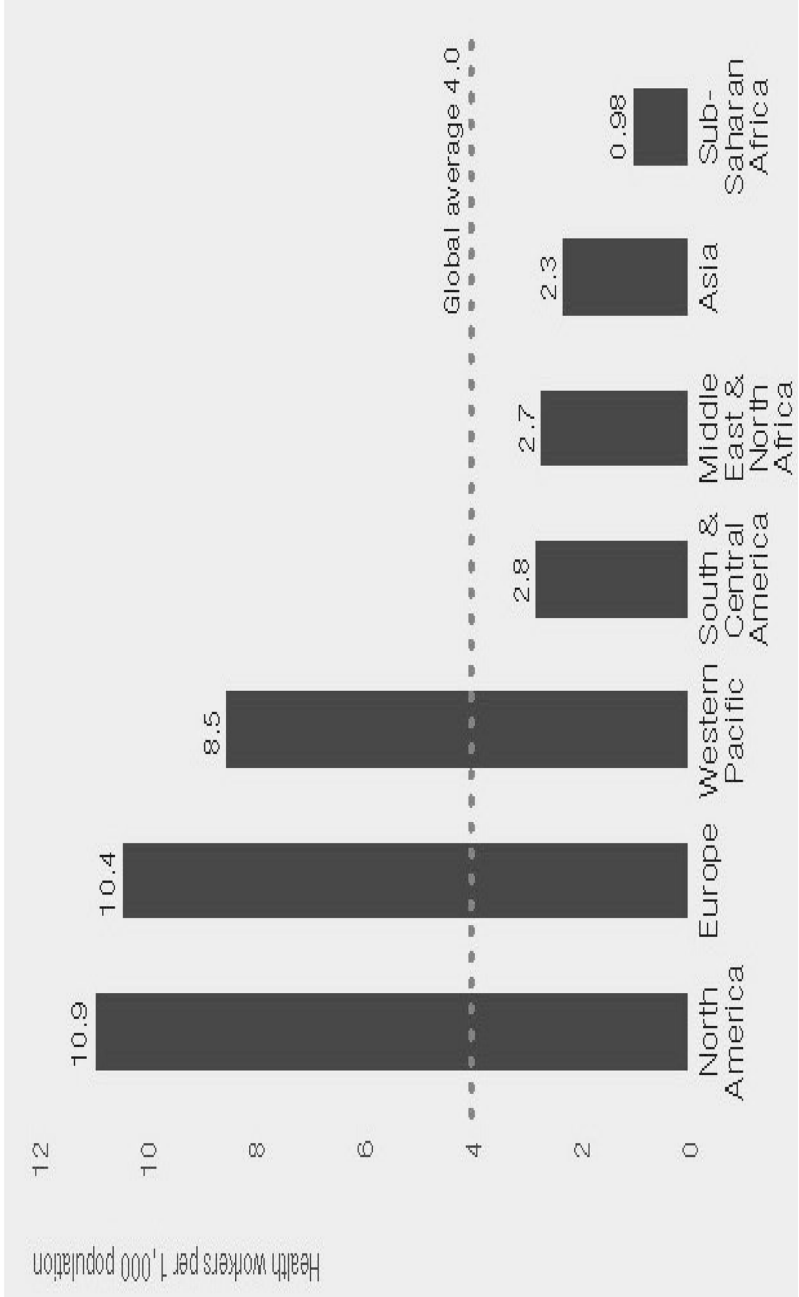


Figure 5.3 Health worker density in different parts of the world. (Source: WHO, 2004).

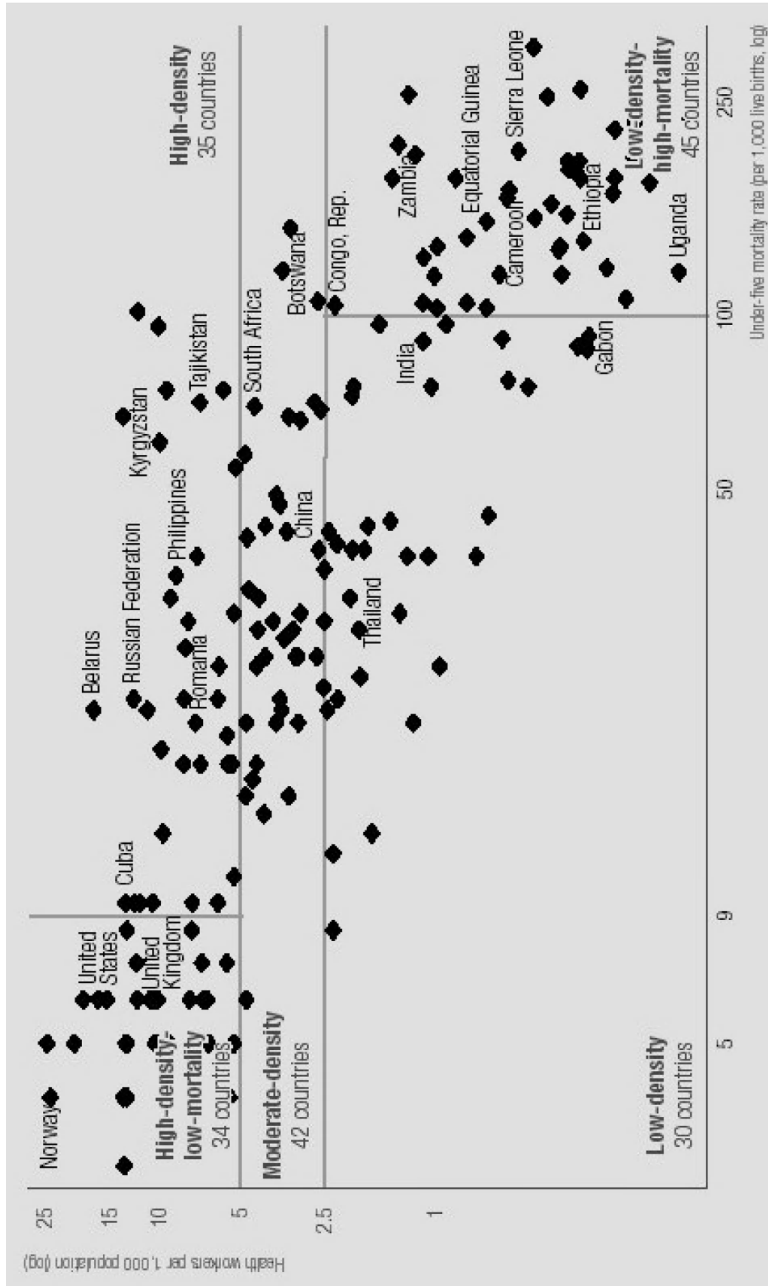


Figure 5.4 Health worker density versus child mortality in different countries.
(Source: WHO, 2004 and UNICEF, 2003).

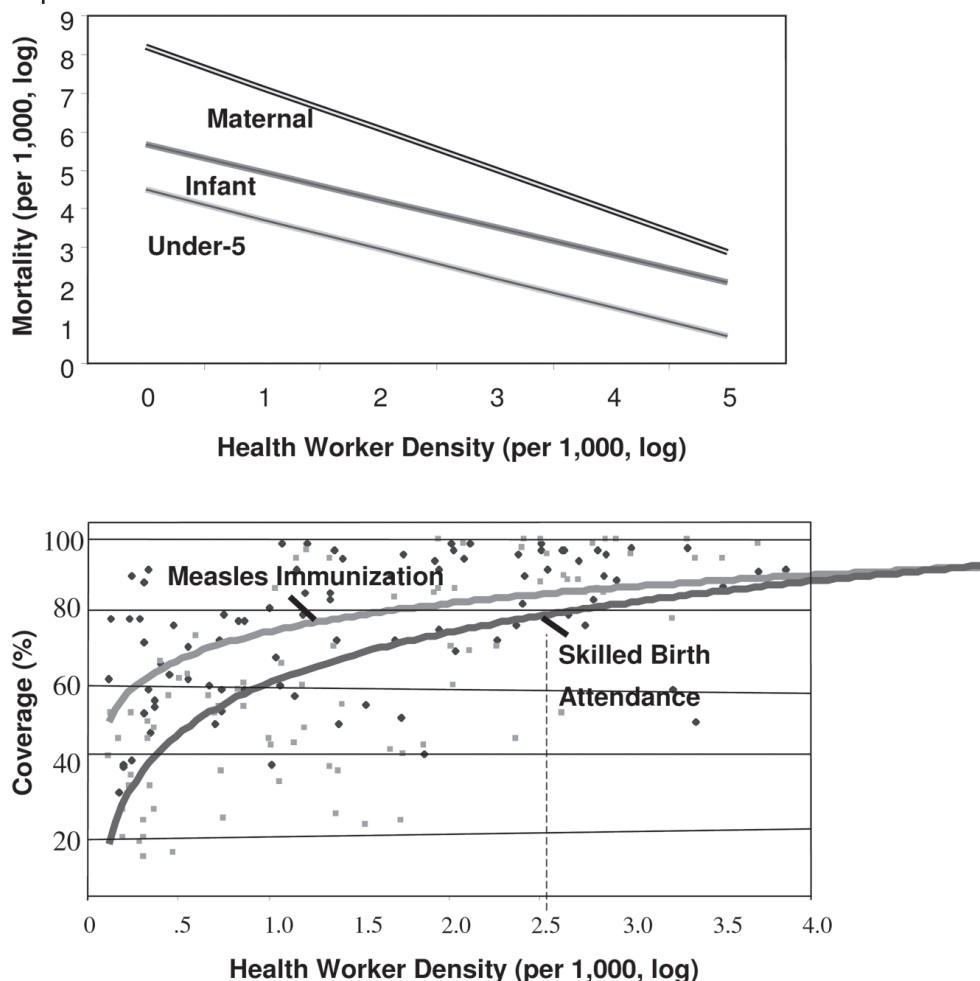


Figure 5.5 Influence of health worker density on service coverage and mortality. (Source: Anand and Baernighausen, JLI, 2004).

Infant mortality is correlated not only to the number of health workers but also to maternal mortality (Figure 5.5, upper). More precisely, immunization is also correlated to the numbers of skilled birth attendants (Figure 5.5, lower). It is difficult to improve results when numbers of health worker are insufficient, as is often the situation today. The difficulty here is that many health workers in developing countries prefer to move to wealthy countries for a better lifestyle. Indicative of this situation was an example of six African countries where, on average, 50% of health workers, if given the opportunity, would move to a wealthy country (Table 5.2).

Table 5.2 Migration intentions of health workers. (Source: WHO, 2002).

Country	Health workers who intend to migrate [%]
Cameroon	49.3
Ghana	61.6
Senegal	37.9
South Africa	58.3
Uganda	26.1
Zimbabwe	68.0

Table 5.3 Projected nursing shortfall in rich countries. (Source: U.S. Government, 2004).

Country	Projected nurse shortfall (year)
United States	500 000 (2015)
Canada	113 000 (2011)
United Kingdom	35 000 (2008)
Australia	31 000 (2006)

The main problem is that, among wealthy countries, an insufficient number of people is trained for work in the health sector, and consequently the shortfall, in nurses alone, is considerable (Table 5.3). There is, therefore, a huge responsibility among wealthy countries to prevent such a “brain drain”, with its very serious consequences for the developing world.

5.4

Financial Resources

In addition to political will, access to vaccination and an adequate infrastructure to mobilize resources, it is clear that in order to improve immunization activities there is also a need to improve the resources themselves. The figures involved are not huge. With 27 million children to be immunized each year, at a maximum average cost of US\$ 30, a total of US\$ 800 million is needed to save more than two million lives. The expectation is that more resources will be needed in the future as new vaccines become available, including rotavirus, pneumococcus, meningitis, and human papilloma virus vaccines. These new vaccines should be introduced during the next few years, and will be of major importance in developing countries. So, it must be ensured that, in the future,

there will not be a 20-year delay between the launch of a new vaccine in wealthy and poor countries. This will be a key indicator of the efficiency of the GAVI, ensuring that in future these new vaccines can be introduced much more quickly – perhaps even at the same time – in both developing and developed countries.

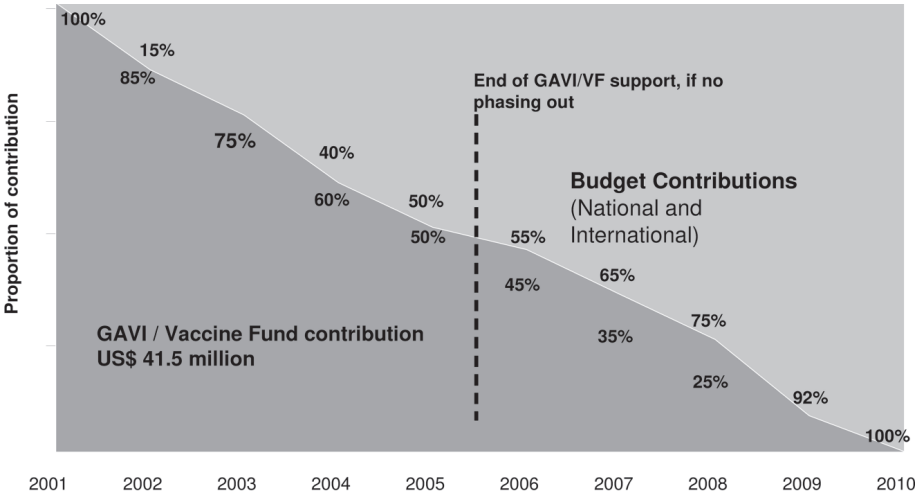


Figure 5.6 Co-financing of vaccination programs: The case of Ghana.

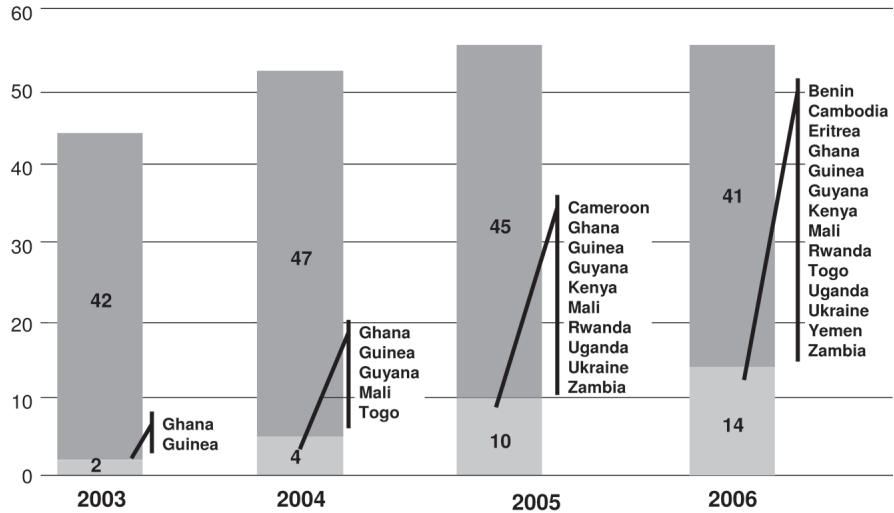


Figure 5.7 Countries co-financing vaccination programs.
Upper bar: countries without government support of the GAVI vaccination program.
Lower bar: countries which co-finance the GAVI vaccination program.
(Source: GAVI secretariat).

The global monitoring of programs will have a positive impact, and increased political commitment should lead to favorable decisions. Figure 5.7 illustrates how, in the case of Ghana, we were able to establish a process by which the country itself plans how to take over from the GAVI, and the initial input that GAVI will give to the program by planning to increase their own resources. For Ghana, the intention is, by the year 2010, to take over themselves the increased efforts on immunization induced by GAVI. The percentage of countries co-financing the vaccination effort remains very low (Figure 5.7), although there is a tendency for countries to take over a substantial part of these additional efforts. Ultimately, this should prove very beneficial for immunization activities.

5.4.1

Sources of Funding

The Vaccine Fund has a clear mission, to obtain more funds from donors, and preferably from international donors. The Fund's mission is to champion, monitor the results of, and help to sustain the efforts of the global alliance in

Table 5.4 Sources of GAVI funds.

<i>Donor</i>	<i>Cumulative commitments (1999–2004) [US\$ million]</i>	<i>Cumulative pledges (2005–2015) [US\$ million]</i>
Bill & Melinda Gates Foundation	758.5	750.0
Canada	13.0	149.5
Denmark	4.5	0.0
European Union	1.0	17.0
France	6.0	12.0
Ireland	2.0	0.0
Luxembourg	0.5	0.5
Miscellaneous private donations	4.0	0.0
Netherlands	71.0	17.0
Norway	102.0	282.0
Sweden	12.5	14.0
UK	51.0	13.5
USA	219.0	64.5
Grand total	1300	1300

order to protect children in the poorest countries. The results have been very encouraging. As of today, the Vaccine Fund has received US\$ 1.3 billion from its inception five years ago, and additional commitments of the same amount of US\$ 1.3 billion (of which the Gates Foundation is contributing about one-half). Whether it is right for a private foundation to represent one-half of the global effort is subject to debate, but we have commitments of another US\$ 1.3 billion for the next few years, and this is important in order to have appropriate visibility (Table 5.4). Some countries are incredibly generous, notably Norway, which has only five million inhabitants. If all countries were to provide the same amount of money per capita as Norway, the situation would be excellent. However, if the current programs are to be carried out with this level of resources, the funding must be improved very substantially. This is particularly the case when financing the newer, technologically complicated vaccines that are inherently more expensive. At present, this financial situation is problematic, and remains a challenge for the GAVI.

5.4.2

The International Finance Facility

The Millennium Development Goals, which were defined by the United Nations in 2000, include as their fourth item the goal of reducing child mortality by two-thirds by the year 2015. To prevent child death through immunization is an integral part of the potential success, but today, the resources flowing to these developing countries in order to make a greater difference remain insufficient. There is a clear need to raise increasing amounts of money at a time when national budgets in many wealthy countries are very limited. The idea of an International Finance Facility (IFF) (Figure 5.8) was developed by the British Chancellor, Gordon Brown. The idea, which in principle is relatively simple, is to create a new financial instrument (the IFF) to which countries would make pledges over long periods of time, perhaps 10, 15 or 20 years. Based on these commitments from donors, the IFF would then offer the prospective of being reimbursed by pledges of future governments. This would lead to a situation in which current effort could be substantially improved whilst still having access to additional resources. These resources would be added to over time, and particularly with regard to the question of access, it would represent a very important mechanism. At the beginning of 2005, the richest governments announced that they would commit US\$ 1.8 billion over 10 years through the IFF, as long as other players matched their contribution. The French government expressed support in principle, proposing that they would secure financing of the additional commitment through an international tax. The IFF concept has raised several questions, and although it is not yet in place, much hope has been placed in its institution.

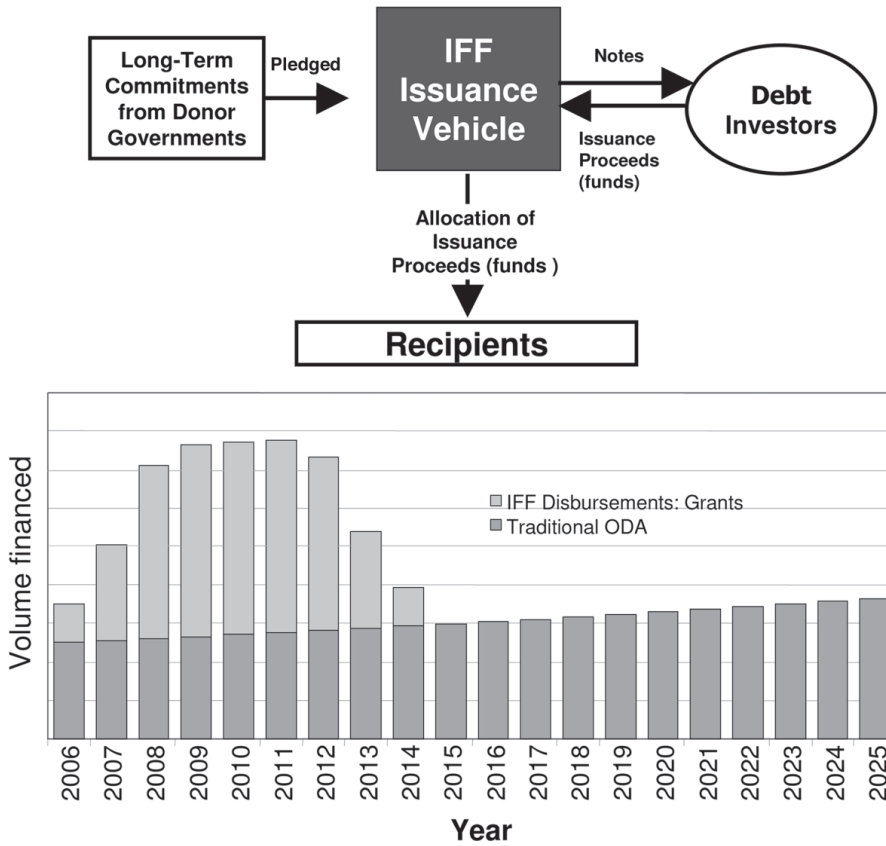


Figure 5.8 A new initiative: The International Finance Facility (IFF).

5.5

A Look into the Future

In closing, brief mention should be made of recent changes and suggested future changes to improve and consolidate these initial successes. Among three points to be raised, the first is that of accountability. The time has gone when financial means could be obtained for developing countries without organizing the system in a way that would be more accountable. Thus, it is important to measure, to check, and to report. Country leadership is also very important, as without leadership nothing can happen. The task is carried out, but in the context of a coordinated approach, much emphasis must be placed within the GAVI to review and check all applications and annual reports. There is also a clear need to ensure that donors are comfortable about how efficiently their money is being used.

The second concept, sustainability, is important because immunization is a long-term undertaking. The improvement of infrastructure is also a long-term task, and countries may encounter difficulties while depending on financial help that, in turn, depends on an annual budget. The Minister of Health in any developing country will generally not know in December how much money will be provided by international health organizations over the next year. Consequently, it is very difficult to propose activities not only for the next year but also over many years. That is why GAVI has introduced the five-year concept.

Finally, industry also requires visibility in order to justify investments in R&D and production capacities, all of which need time to be recouped. Thus, it is necessary to provide the corresponding visibility in terms of financial resources available to buy the product.

Accountability, sustainability and innovation form the basis for the GAVI. The GAVI, as a global alliance, brings together all players at national and international levels, NGOs, foundations, and scientific bodies in order to optimize the global efficiency of all concerned, and in this respect industry is an important player. The GAVI involves industry to a great degree, whereas the Global Fund to fight AIDS, Tuberculosis and Malaria prefers to take another route. Having industry on board is an important factor since, in the way that situations are managed and accountability is built up, much emphasis is placed on the notion of a contractual approach with countries based on multi-year plans. Consequently, the decisions are made by countries based on evidence, and contributions will depend on the results achieved by those countries. Last, but not least, the question of advocacy and resource mobilization should be shared by the global community.

Whilst advocacy and resource mobilization is the mission of the Vaccine Fund, we are all part of the global process to ensure that resources are made available. Clearly, progress has been made, but there is still a long way to go. The opportunity exists to provide access to basic protection for almost all children worldwide. During the past four years, Nelson Mandela has served as the chairman of the Vaccine Fund's board, and remains convinced that immunization is the basic right of every child. Moreover, he is convinced that because we have the tools to protect these children, because we know how to do it, and because the necessary resources are relatively limited, we should all – individually and collectively – bear part of the global responsibility to ensure that the task is completed.

Author Biography

Jean Stephenne



President and General Manager, GlaxoSmithKline Biologicals

Jean Stephenne has overseen GlaxoSmithKline Biologicals since 1991, serving as Vice President and General Manager, then Senior Vice President and General Manager, until his appointment as President and General Manager in 1998. Prior to this, he was Vice President of Human Vaccines Research and Development and Production from 1988 to 1991. Jean Stephenne joined the company in 1974 as head of bacterial and viral vaccines production, becoming Vaccine Production Director in 1980. He served in a variety of capacities as Vaccine Plant Director and R&D Director from 1981 to 1991. He has a degree as engineer in Chemistry and Bioindustries from the University of Gembloux (Belgium) in 1972 and obtained a degree in Management from the University of Louvain, Belgium. He has served as President of the Union of French Speaking Companies (1998–2000), is a member of the European Association of Vaccines Producers, and a member of the Management Committee of the Belgian Companies Federation. He is also a member of the Board of several Belgian companies.

6

Meeting the Challenges of Manufacture and Delivery of Affordable Vaccines

Jean Stephenne

6.1

Introduction

In the preceding chapters, much has been said of the progress being made in the development and affordability of vaccines, and how people are beginning to recognize the value of vaccines in society. Here, the subjects to be discussed are the values of vaccines, their manufacture, and R&D developments in this field.

The lack of progress in vaccination schemes that we are experiencing is due largely to an ongoing discussion of the value of vaccines, rather than to their being recognized as a “right to life”, in both developed and developing countries (Figure 6.1).

Today, nobody recognizes that value, and that perception must be changed. Indeed, it is the responsibility of society to recognize the value of vaccines, and this must be based on the contributions that vaccines make to quality of life in society. Currently, 26 diseases are vaccine-preventable, and it has been



Figure 6.1 The global vaccine market.

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on two occasions that “herd immunity” has been acquired, in the case of meningitis C and streptococcus pneumoniae. The progress is hampered, however, by what might be considered individualism in society, and why some people have the right to refuse vaccination. It is understandable that some people may refuse vaccination, but in doing so they are putting at risk others within that society, and this aspect must be recognized. In the United States there is a clear liability to vaccination, and debate will continue with regard to those who refuse vaccination and their liability towards society. Last year, GlaxoSmithKline (GSK) – and probably many other vaccine producers – spent many millions of dollars defending themselves against possible litigations in the United States. In fact, this is the main reason why the vaccine industry has largely diminished since the 1970s. The question is, can the debate be restarted in the coming years? There is indeed a risk, particularly in the United States, that debate will return, and this point must be addressed if there is a desire to defend the value of vaccines. Within the past 20 years, GSK has taken the view that the global market is not restricted to the children of Europe and United States, but includes all the children of the world. Access to vaccine must be made available to all in the future.

6.1.1

Market Challenges

The modern vaccine market faces many challenges, because when man travels through society, infectious diseases travel with him. This important point must be remembered, because only 50 years ago, if an influenza pandemic occurred, the procedure was to place infected people into quarantine. Fortunately, that situation no longer applies, but if infectious diseases are returning, then preventive measures must be considered, and vaccination surely offers the best protection. Consequently, R&D investment in vaccines will be required to supply the needs of the developed and developing world. It is essential that manufacturing follows demand, and that there are immediately available stocks of vaccine worldwide. It is for this reason that GSK proposed the launch of its rotavirus vaccine first in Mexico, in an attempt to persuade the Mexican government to accept their responsibilities and not always to complain about the vaccine industry, that there is insufficient investment in vaccine production. In industry, it is essential that reasonable margins are incorporated: where once the subject was dual pricing, it is now three-tier pricing, and this is the key to continued investment in vaccine production.

6.2

Vaccine Research and Development

Although many consider vaccines to be cheap, this is simply not true. Today, the total cost of developing a modern vaccine, and conducting the appropriate testing, is rapidly approaching US\$ 1 billion (Figure 6.2). For example, the anti-malaria vaccine which began development in 1982, and if launched in 2009–2010, will have cost more than US\$ 1 billion to bring to market. This level of cost requires the co-operation of others, in this case the Walter Reed Hospital and many other scientific institutions, otherwise the whole procedure cannot be conceived. The illustration in Figure 6.2 provides three messages. First, the preparation of a DNA vaccine or live vector constitutes only a very small portion of the process in relation to the overall project. Second, it is relatively easy to induce an immune response, but to obtain an effective immune response remains a challenge. Immunity is often a lot more complex than people assume, and this is convincingly demonstrated by the examples given by Sir Gustav Nossal in Chapter 4. Third, it is important not to repeat the mistakes with the HIV vaccine, when, due to public pressure, there was a rush to conduct large clinical studies with conjugated vaccines that ultimately failed. It follows that correct science must be instituted before clinical trials are considered.

In the past, the vaccine industry has suffered attacks from both the scientific community and civilian society on the basis that it was not conducting

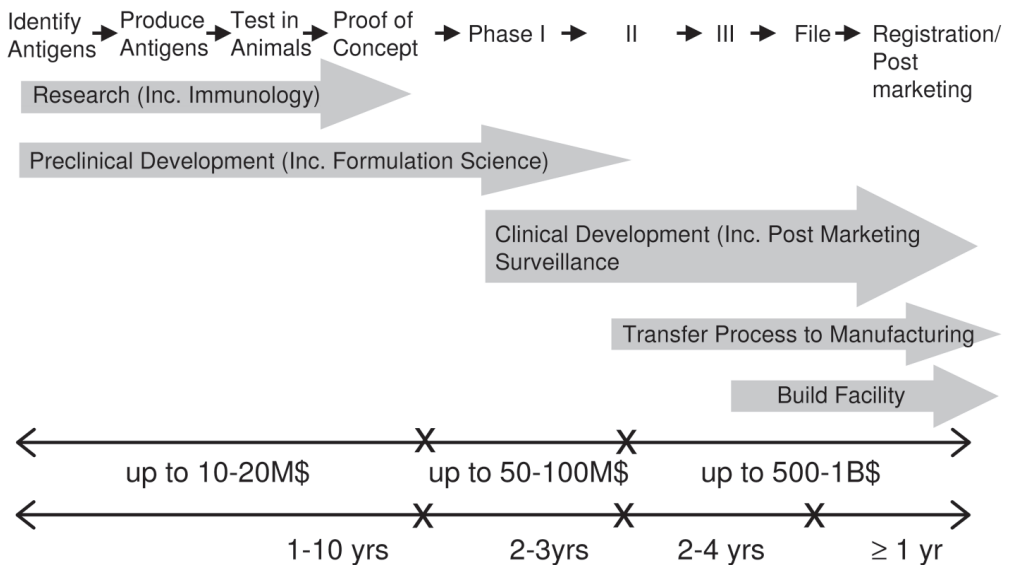


Figure 6.2 The Research & Development pipeline for new vaccines.

<u>Pre-clinical</u>	<u>Phase I</u>	<u>Phase II</u>	<u>Phase III / Filed</u>
RSV	Flu improved	EBV	N.Meningitis combinations
CMV	HIV	Malaria	Rotarix TM (Rotavirus)
Men B (paed)	S.Pneumoniae (elderly)	Hepatitis E	Streptorix TM (Strepto)
Chlamydia	TB	Dengue	Cervarix TM (HPV)
Staph Aureus	Zoster		Priorix tetra TM (MMRV)
SARS	Flu pandemic		Simplirix TM (Herpes)
Cancer	Prostate Cancer	Staph. Antibodies (Mab)	Boostrix TM IPV (dtpa IPV)
Allergy	Breast Cancer	Lung Cancer	Fendrix TM (HepB hemodialysis)
	Melanoma		
Total = 8	Total = 8	Total = 7	Total = 8

Figure 6.3 Vaccines in the pipeline at GSK Biologicals.

RSV = respiratory syncytial virus; EBV = Epstein-Barr virus; VZV = varicella zoster virus.

sufficient R&D in the vaccine field. It can certainly be said that for the GSK pipeline – and this applies equally to the pipeline of any vaccine-producing company – there is today a vaccine under development for all diseases of the developed and developing worlds, and that complaints of inadequate R&D in the industry are no longer justified and should be reassessed (Figure 6.3). It is now the responsibility of the governments of the developing countries and the G-8 states to provide support, since if vaccine development is to be pursued then there must ultimately be a market for that development to pursue. If this is not the case, then the industry will certainly starve. Of course, the major question today is how will society pay for the 20 new vaccines that will be launched during the next 10 years? This is true not only in developing countries, but also in Europe and the USA. If the value of vaccines is not recognized, then the objective will not be achieved, and the tenet that the control and prevention of infectious disease is better than cure will not be upheld.

6.3

Vaccine Manufacture

Vaccine manufacture is a highly complex process, and it is important that this point is recognized. Producing vaccines was my first task when I joined the vaccine industry, and then as now it remains the most complex task the industry has to offer. In order to produce a modern vaccine, and then to license it, the decision to invest in the manufacturing process must be taken some five years before the launch. On occasion, it may take over a year to produce a

vaccine and release it. Typically, during production there will be batch-to-batch deviations, mainly because when working with live microorganisms, deviation is “normal”. It must then be determined whether this deviation affects the quality of the vaccine, or not. This problem in its entirety is almost impossible to solve, not only because the system is highly complex but also because the health authorities do not understand such complexity. The authorities will produce a rule-book, but they do not understand the biology behind vaccine manufacture. Twenty years ago, inspections were carried out by biologists, but today’s inspections are carried out by people who know the rules but do not understand what they are inspecting. This presents a major problem that must be solved. On the other hand, the industry must bear the responsibility of maintaining up-to-date systems, so that they are not producing vaccines with a plant that was built 20 or 50 years ago. The technology involved is rapidly changing, and the role of the regulators (including WHO) is to indicate when modern technology should be introduced into the process. The role of the regulator is also to understand and finalize a process, and in this respect they must organize and schedule their inspections so that production-line accidents, as have happened during recent years, may be eliminated.

So, the vaccine-producers as a group are requesting an open and constructive relationship with authorities, who in turn should not be afraid of discussing and proposing change, rather than threatening the closure of a facility, as is often the case. For this system to succeed, the main requirement is long-term planning, and recent developments with UNICEF have led to major improvements in this area. As vaccine manufacture is highly complex, it is reasonable to seek three- and five-year forecasts, rather than to operate on a day-to-day basis, and in this way it will be possible to build vaccine stockpiles in case of emergency. Finally, as is the case of the automobile industry where Renault and Volkswagen, for example, have plants in China and India, the vaccine industry will ultimately have plants situated around the world. In this way, it will be feasible for GSK and other vaccine producers to impose the same standards in the developing world as they do in Europe or in the United States. Given the opportunity, such globalization of manufacture could be undertaken very rapidly.

6.4

The Vaccine Marketplace

In the past, the marketing of vaccines often included a launch in Europe and the US, followed some 20 years later by extension of the market into developing countries. This concept must change. A new system is needed in which the vaccine is launched worldwide, in both the private and the public markets. For developing countries, a partnership is needed in order for the industry to

continue to invest in vaccine production for the developing world, and support is also needed in areas of R&D. In addition, there is also a need to establish credible markets in these developing countries. As Dr. Martin suggested in Chapter 5, if there is no sustainability, it is likely that the process will not work. It is at this point that the initiative of the British Chancellor, Gordon Brown, should be applauded, in aiming towards a pre-purchase agreement with the vaccine industry.

6.5

Vaccine Availability

I believe that the provision of vaccines free of charge to the entire population is not sustainable for society in general. The main crisis here would be the cost to social security services, as governments are unlikely to continue offering vaccines free of charge to developed countries. The problem is that such a system would have no accountability, and in the public opinion anything that is provided free of charge has no value, and so the system will need to be changed. It is likely that, before 2010, there will be six or seven new vaccines available which Europe is not ready to fund, the United States will probably not fund, and developing countries are simply unable to fund. This will also mean that new vaccines are available for segments of the population other than infants – there will be vaccines for the elderly, for adults, and also for adolescents. Thus, the financial pressure on the community to spend more on disease prevention will increase. Today, only 1.2–1.5% of the global expenditure for pharmaceuticals is spent on vaccination. This percentage must be increased dramatically over the years to come. In terms of vaccine availability, the aim is to provide vaccines to the developed and developing countries, to all segments of the population, and in turn to create market segmentation (Figure 6.4). In India, for example, some people can afford vaccines but do not pay for them, because these are provided for free by UNICEF or WHO. The governments must also take responsibility, and in truth the private and public systems must coexist. In future, there will be an increase in manufacturing capacity, and GSK will clearly invest in all major countries. With plants currently operational in China and India, vaccine manufacture will be continued. And, as with the automobile industry, where needs exist there will be differential pricing. In this way, GSK is looking to the future market and market segmentation, and this must be carried out in cooperation with governments as our company cannot do this alone. The segment at the bottom of Figure 6.4 is termed ‘funded’; in other words, a mechanism must be found whereby a wealthy country will help to provide the vaccine for a poorer country (a ‘poor’ country would be defined as having an annual GDP below 600 dollars per inhabitant), and this is the goal of the

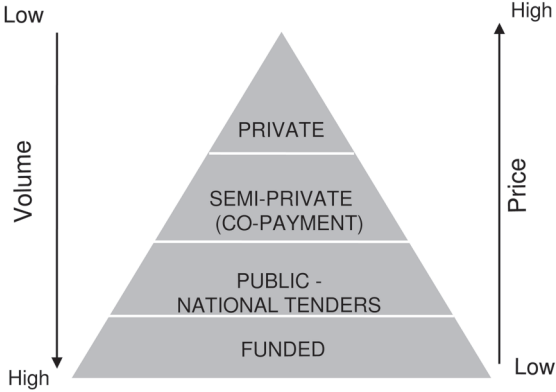


Figure 6.4 Vaccine market segmentation.

Gates Foundation. I applaud what Bill Gates is achieving through his foundation, but as has been already pointed out in Chapter 5, it should not be the case where an individual person provides for half of the funds needed; rather it is the responsibility of the governments of the wealthy countries. To demonstrate what the reality is today, three examples – rotavirus, human papilloma virus, and malaria – will subsequently be examined.

6.5.1
Rotavirus

Rotavirus (Figure 6.5) kills 500 000 children each year, but effective vaccines are becoming available, and at GSK two standards are currently under development. Our first vaccine had been developed in Mexico, and has been launched there at the standard of the U.S. and Europe. Studies were conducted

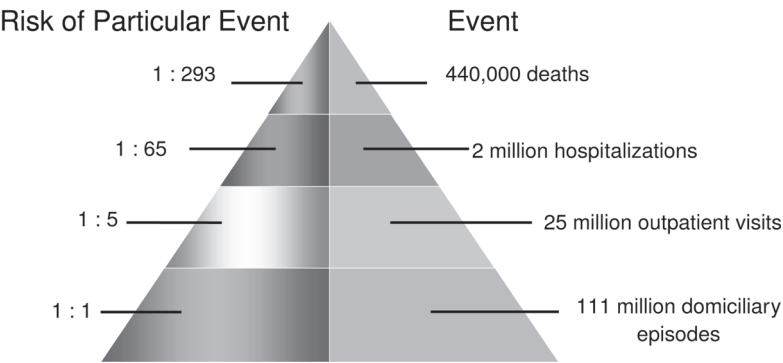


Figure 6.5 Estimated global prevalence of rotavirus disease.
(Source: Parashar et al., *Emerg. Infect. Dis.* 9, 565–572, 2003).

in 100 000 children – perhaps the first time that a vaccine has been studied in so many children – and the vaccine is now available, though whether it will be used is unclear. To illustrate this, the parameters of the disease must be considered. Rotavirus is a democratic disease, and whether people live in developed or developing countries, they will contract it. However, whereas 1 in 300 children contracting rotavirus will die from it in developing countries, this will not be the case in Europe and the US. Nonetheless, since in Europe and the US 50% of hospitalizations during winter are due to rotavirus, there is a clear medical need, and it will be interesting to see how society implements this vaccine.

6.5.2

Human Papilloma Virus (HPV)

In the treatment of cervical cancer, a vaccine will be launched worldwide in 2007 and, in theory, should be administered to immunize 1.6 billion women. This is the target, and it is the responsibility of government to ensure vaccination. Clearly, a mixture of private and public financing will be required, but it must be remembered that cervical cancer is the second most prevalent cancer in women worldwide. During the past 30 years, no single vaccine has ever been 100% effective, but the HPV vaccine retains 100% efficacy at three, and even perhaps four, years after immunization (Figure 6.6). The medical costs of the disease are huge, and they could be saved by using the vaccine (Figure 6.7). However, it must then be ensured that the savings are reallocated to vaccine purchase, and not used elsewhere. Indeed, this will be the main challenge when the vaccine is launched.

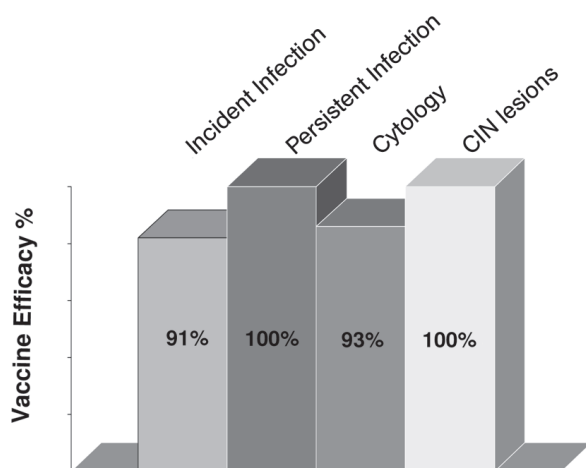


Figure 6.6 Efficacy of the HPV-001 human papilloma virus vaccine.
(Source: Harper et al., *Lancet* 364, 1757–1765, 2004).

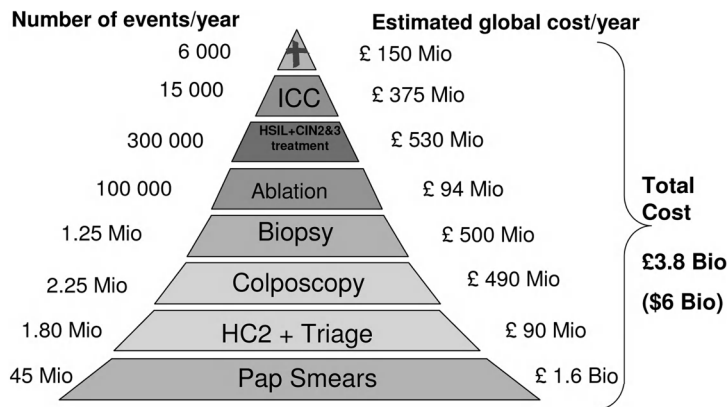


Figure 6.7 Costs associated with HPV in the United States.

6.5.3 Malaria

The malaria vaccine represents an excellent example of public-private partnership and indeed, without collaboration with Walter Reed Hospital (US army) and the Gates Foundation, its development would not have been possible. The disease is limited to the poorest countries – there is no other market (Figure 6.8). Historically, the development of malarial vaccine extends back 84 years, while the GSK program was started more than 20 years ago, in 1982 (Figure 6.9). The reasons for our sustained effort to develop this vaccine are two-fold. The first reason was to develop a malaria vaccine; the second reason was that malaria has provided various means of improving and increasing scientific knowledge in immunology and infectious disease for the future. Hopefully, the vaccine will be launched in 2009, and will provide about 58% protection against severe disease in the cohort of one to four years. However, when examining the outcome under two years, the protection against severe disease is already 77% (Table 6.1). Now, the focus will be to conduct a major clinical study in children aged between 2 and 18 months, where efficacy of the vaccine would surely be higher and this will have a major impact on public health.

Table 6.1 Results of the RTS,S vaccine trial in Mozambique.
(Source: Alonso et al., Lancet 364, 1411–1420, 2004).

Condition	Mean vaccine efficacy [%]	95% confidence interval
Infection	45	31–56%, p < 0.001
Clinical disease	30	11–45%, p = 0.004
Severe disease	58	15–79%, p = 0.019
Severe disease (first 24 months)	77	27–97%, p = 0.018

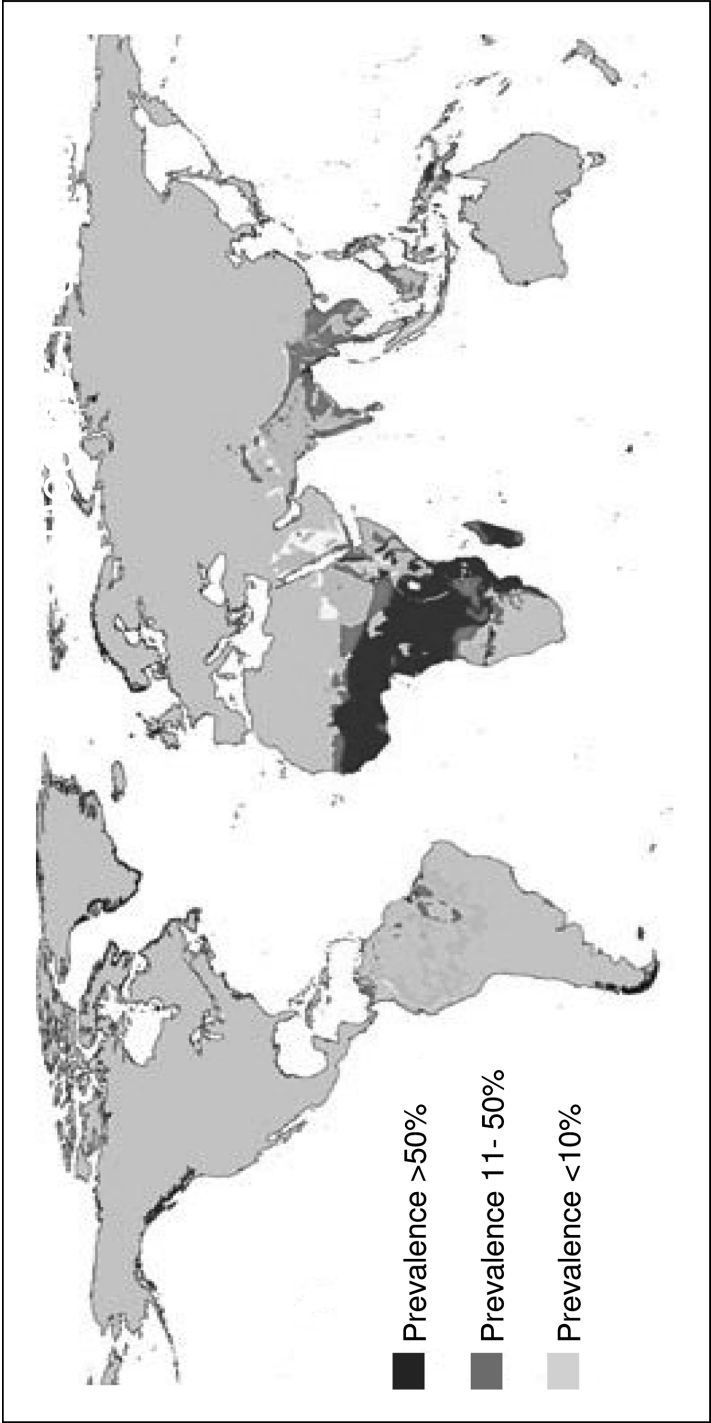


Figure 6.8 Global distribution of *Falciparum* malaria.
(Source: Snow et al., Nature 434, 214, 2005; Sachs et al., Nature 415, 680, 2002).

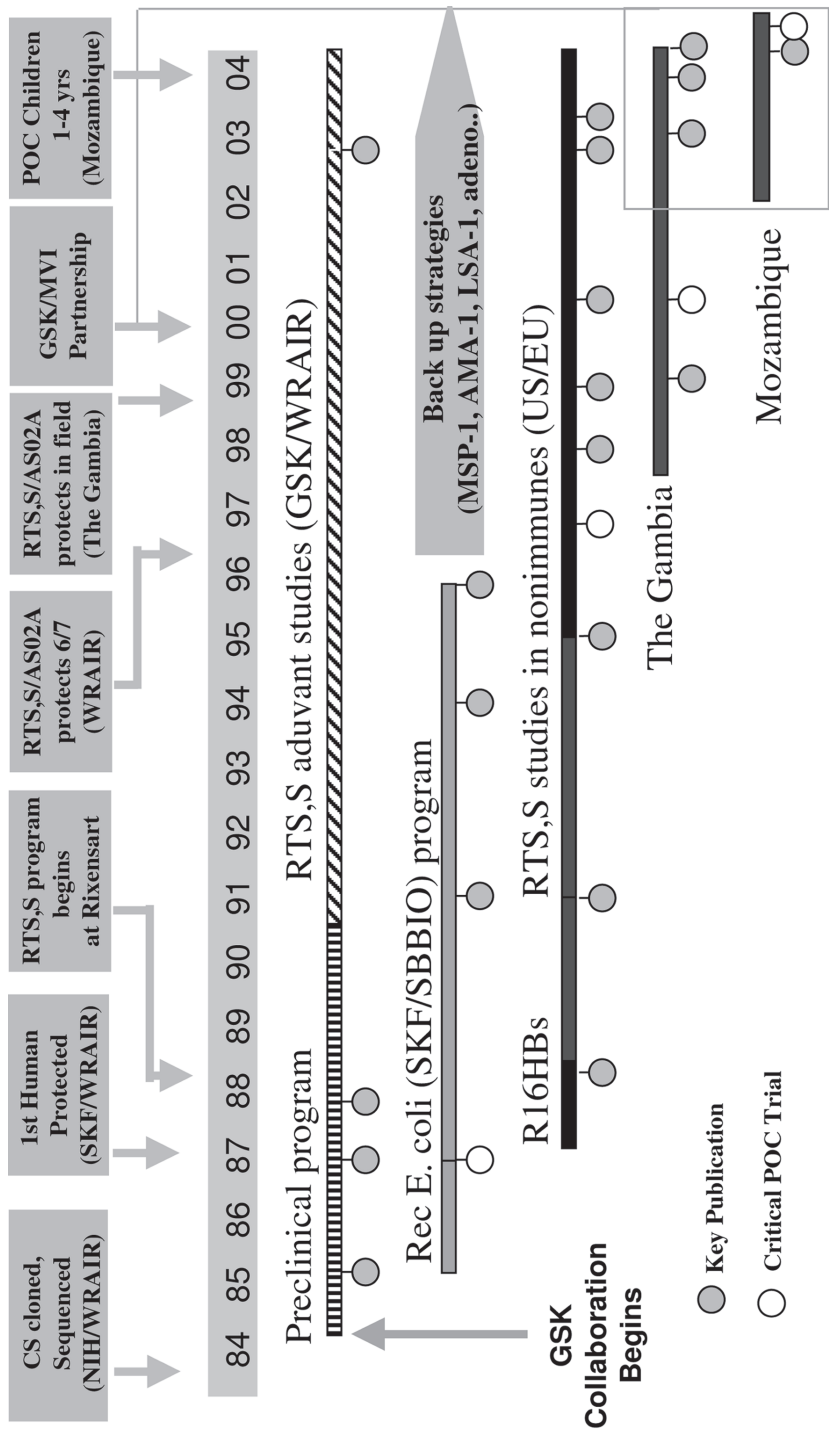


Figure 6.9 History of the RTS,S malaria vaccine program.

6.6

Conclusions

On 28th February 2005, in his budget speech, the Minister of Finance of India stated that, “India is not a poor country. Yet a significant proportion of our people are poor”. Whether India is poor is open to discussion, because there are people in India who have money, who can purchase modern vaccines, and who must invest in purchasing vaccines. But there must also be in India a responsibility of the government to purchase certain vaccines for the poorest. If the government accepts this responsibility, then the G-8 group can help them to achieve this. In India, there are three main groups responsible for payment: the wealthy among the Indian population; the federal government; or the local government, who must also pay for the poorest, and this is where the G-8 group can help. This is the preferred type of partnership for vaccination, and is what must be sought. However, if there is no accountability, this approach will fail. The advantage of the Gates Foundation and the Vaccine Fund is that they have created accountability, and it is important that, in India, both the Minister of Finance and the Minister of Health recognize in their budget process that vaccination is important.

In conclusion, it appears the R&D community and the industry have done their job, and now the baton is being passed to others to continue the fight. It must also be realized that vaccine manufacture is a complex process and that industry and the authorities must generate a positive dialogue. If this cannot be achieved, then major crises, as occurred in 2004 for the influenza epidemic, will undoubtedly recur. This is a critical point, because it is necessary not only to change the way that the biomedical industry functions but also to ensure an ongoing dialogue to ensure increased output and quality control on a worldwide basis. Also under debate is whether the value of vaccines will be recognized in each country. This relates to both developing and developed countries alike, and in future vaccines should be regarded as an investment, similar to that of education, in order for society to progress. The final question is whether the G-8 powers and other governments will apply the new model to the cases for rotavirus, HPV, and malaria. This is the next major challenge, and it seems certain that the model will be applied also to *streptococcus pneumoniae*, and perhaps later for dengue fever. This is the challenge, and it is here now.

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Module III

Bioethics: What is the Tradeoff Between Principles and People?

Introduction

Dominique Lecourt

The success of innovations in vaccines rests on the technological capacity of innovation, the productivity of the vaccine industry, and the conquest of new markets. However, medical treatment of the human body set in highly diverse cultural contexts necessitates careful attention to ethics. In the case of sub-Saharan Africa this point of view merits even closer scrutiny. The progress of clinical trials which proceed there must be followed rigorously to ensure the enlightened assent of the subjects which is freely obtained, and that the populations concerned will be able to profit from any favourable result. But how far should we go in promoting this regulation? Companies are increasingly risk-averse, and are likely to slow the development of vaccines in keeping with increased regulatory oversight. Once again the commitment of politicians is as important as that of economic decision makers. They must ensure that the general public is able to advocate for their own health by including, understanding and supporting the efforts of scientists and the industrialists.

Author Biography

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Philippe Kourilsky received a doctorate from l'Ecole Polytechnique. In 1972, he joined the Institut Pasteur serving as the director of the Molecular Biology Unit in 1979 and as the director of research from 1992 to 1995. He was named a professor at the Institute in 1993, and in 1998 he was also named a professor at the College de France where he holds the chair of Molecular Immunology. In 2000, he became the general director of the Institut Pasteur. He is a member of the French Academy of Sciences.

7

Are First-World Ethics Applicable to the Third World?

Philippe Kourilsky

7.1

Introduction

In human health, less than 10% of R&D resources are devoted to diseases that involve 90% of the world's population. More than two billion people suffer from infectious diseases for which vaccines and drugs are not available, because they are too expensive, because they cannot be adequately distributed, or because they simply do not exist. The R&D pipelines which could – and should – provide adequate vaccines and drugs for such neglected diseases, face major difficulties. Contrary to common thinking, funding is not the only issue, as research, regulations and ethics each share in the unacceptable situation endured by almost half of the world's population. In fact, the numbers of disadvantaged are absolutely huge, numbering billions among the human population.

7.2

The “90–10 Gap”

The problems faced today are double-faced. First, there is the problem of distributing existing vaccines and drugs, and it is quite well-known – and incredibly scandalous – that the measles vaccine which costs only a few cents and has used for decades is still not distributed to the extent that several hundred thousand children die every year. The second issue is that of R&D. This problem is referred to as the “90–10 gap”, which means that 90% of disadvantaged people benefit from less than 10% of the worldwide biochemical and biomedical research (Figure 7.1).

Effort in terms of R&D is very much focused on the diseases that affect the developed world; for example, much more money is spent on prostate cancer

- **90 % of the diseased people benefit from less than 10 % of the worldwide biomedical research**
- **1 % of the 1400 new drugs which have reached the market in the last 25 years are devoted to the so-called “neglected diseases”**

Figure 7.1 The “90–10 gap”.

than on tuberculosis. As a result, only 1% of the 1400 new drugs that have reached the market during the past 25 years are devoted to the so-called neglected diseases – that is, diseases of the poor. Consequently, R&D is not providing the medical solutions for very large numbers of people. Thus, it is not only the correct distribution of existing products in the developing world that is lacking, but also several products needed to cure diseases in the developing world. It must be emphasized that, during the past 25 years, worldwide funding in R&D has increased at least three- to five-fold, and on that basis it cannot be argued that there is insufficient money available. Rather, it is the way in which that money has been distributed which is in question. In other words, there is a structural problem that needs to be understood.

Research is to a significant extent (but not entirely so) market-independent, whereas development is to a large extent market-dependent. In other words, academia is virtually free to do what it wants in research, and in areas that it wants to explore. Governments provide a very strong stimulus when allocating resources within academia for a certain type of investigation. The question should also be raised with regard to the role of charitable money in the promotion of research; for example, much more charity money is donated for research into cancer than into infectious disease. However, research is basically or largely market-independent and in academia – for example, in the Pasteur Institute and elsewhere – there is freedom to work on diseases for which there is no drug market. This is not the case for development which is, to a very large extent, market-dependent. Consequently, the problem is one of how to finance studies, with development costs being at least ten-fold those of the research. In today’s world, the development costs of a new drug are estimated to be approximately 500 million Euro. Likewise, the costs to develop a vaccine have increased significantly, and are now similar to those for a drug, with huge amounts of money being spent in order to reach the marketplace. This is especially problematic for the neglected diseases, because if there is no marketplace then there is no new medicine. The research may be conducted, but there are no drugs or vaccines to follow. At the Pasteur Institute, a large proportion (up to half) of the research effort – even if successful – will never be developed into real products usable in the developing

world, because development funds are lacking. The basic problem is that, in an ongoing research program, development will not fall within the current funding system and products will not be generated. For the neglected diseases this represents a major disaster, the conclusion being that research is neglected to a certain extent, notably in areas of exotic parasitism, such as filariasis.

7.3

Vaccine Production

Vaccines are a neglected part of the pharmaceutical industry in the sense that they represent less than 3% of the total drug market. If a projection is made based on the fact that vaccine-producing companies spend exactly the same fraction of their money on R&D, then the industrial money available for vaccine development should be about 3% of what is available to develop drugs. Put this way, it may not be surprising that, as yet, there are no vaccines available to combat HIV while antiretroviral drugs have, fortunately, been made available almost ten years ago. Although it would appear that the funds made available for HIV vaccine development are insufficient, this is not accepted by all, and it is also true that an HIV vaccine involves specific and difficult research problems that must be addressed.

Until recently, the manufacture of products resulting from R&D projects was mainly carried out in the developed countries. The cost of the product incorporates the cost of R&D, which means that the cost structure is modeled by the developed countries and not by the developing countries. This cost structure is clearly inadequate for developing countries, however. A major point here is the impact of regulatory standards. It is acknowledged by the major pharmaceutical companies that development costs have increased three-fold during the past 15 years, and this is especially the case for vaccines. The question to be asked, then, is whether this increase is justified, and why. In fact, the rise in costs is mainly linked to a demand for increased safety among the general public, and is reflected in many processes. Today, for example, liability problems in developed countries have become very significant, with companies withdrawing drugs as soon as any safety problem appears. Often, the withdrawal is upheld even when the situation is manageable, for fear of the company being sued and losing very large amounts of money.

The consequences of this for the developing countries are numerous. For example, as standards change almost daily a “race” is developing that they cannot keep up with. The regulatory agencies seem to compete with each other, with the European agency, the EMEA, wanting to perform as many good deeds as the FDA. As new technologies are developed, it is temptingly normal to introduce new analytical methods in an attempt to achieve improved purity, characterization, etc. The problem is that the developing countries

cannot maintain the pace. Accordingly, they face a highly efficient protectionist barrier against the export of health products to the industrialized countries of the North. This is very different from buying a shirt or a suit, many of which are now produced in China, the point being that the drug industries of the western world are very well protected by their regulatory standards.

7.4

The Ethics of Regulatory Standards

One particular issue is that when paying for the drugs and vaccines manufactured in the developed world, the developing countries suffer from inadequate cost structure. In other words, they pay for the R&D and for manufacturing performed along the standards of the rich countries. This can be partly corrected by the differential pricing policies being set forth, but this is a relatively recent proposal, except for vaccines. The developing countries often apply the same standards to themselves because they do not want to appear inferior to the rest of the world. As a result, they increase their own problem-solving approaches, and this may have dire final consequences. The R&D costs for vaccines and drugs that are specific to neglected diseases are beyond the available means of all. In fact, they are beyond the available means of the countries in which these products are needed, as well those of most nongovernmental organizations (NGOs) and of the international organizations themselves. Put another way, if 50 products are needed, and each requires about US\$ 1 billion for development, the money is simply not available worldwide. One point that should be emphasized here is the belief that many people have, that regulatory standards fit the ethic. In other words, there is an implicit ethical dimension in regulatory standards, which can be stated in very simple terms that “safer is better”. In general, people do believe that safer is better, and that this is the ethical statement. Today, however, it is unclear to what extent safer is obviously better, and how such a statement can be introduced into a cost benefit analysis which has been adapted to the real world.

In the modern, global world there is a clear trend towards the globalization of standards, with pressure being applied constantly to achieve this goal. There are very many reasons for this proposal, some are technical, and others political. The ethical movements, or at least part of the ethics thinking in the world, is termed “universalist”, and this now claims that the ethical principles should be worldwide. Although it is unquestionable that health standards should be the same in all parts of the world – and the achievement of this goal would be excellent – it is so far away as to be totally unrealistic. Indeed, it could be considered unethical to imagine that this might be the case in the short term.

7.5

Challenging Regulatory Standards

One final question relates to whether regulatory standards should be challenged. The most likely answer to this is “yes”, because the benefits and costs incurred are poorly evaluated (if at all), and this is especially shocking for scientists. It is amazing to see that these regulations have varied over time, and that the costs have multiplied by a factor of two to three, and yet there is no evaluation. In the case of vaccines, most people living today have been treated with vaccines that today would most likely be claimed as inadequate, because they would not match the standards. For example, BCG is a very old vaccine that is known not to be perfect, and it is accepted that a better tuberculosis vaccine is needed. The BCG vaccine provokes a very small number of accidents termed BCG-itis in children, and consequently the claim has been made that the vaccine should be improved, or better purified. In fact, the cohort of children who contract BCG-itis has been studied, with remarkable results. All children who developed the condition were found to have mutations in the immune system which were revealed by vaccination. In a way, they were immunodeficient, but this had not been noticed because it was only a slight immunodeficiency that was revealed by the vaccination. To put this another way, the safety of the vaccine cannot be improved; the problem is not due to the vaccine’s characteristics, but simply to genetic variation among the human population.

It is thus clear that the regulatory standards must be challenged in order to determine why the costs are so high, and what benefits are obtained. This is especially important for the developing countries, as elsewhere in the world the cost of health is growing, and all governments will attempt to limit the public costs. Even in the developed countries it is important to determine how and when the money is spent, since the social security systems are limited in the amounts they can pay. Challenging the regulatory standards does not imply any relaxation in scientific rigor; on the contrary, it provides a better indication of what is being done and whether it is being done properly.

Surprisingly enough, regulatory standards have their share of responsibility in unacceptable health situations in the developing world. R&D costs cannot be borne by poor countries, academic institutions, NGOs, or even international organizations. The budget of the Global Alliance for Vaccines and Immunization (GAVI), which is 1.5 billion US\$ over a five-year period, would allow for the development of two molecules or two vaccines. The issue is whether such funding is sufficient. A recent directive involved the creation of a new NGO termed the Drugs for Neglected Disease Initiative (DNDi), the business plan of which was created by Doctors Without Borders, together with the Pasteur Institute and various other organizations. The business plan is to

produce eight new molecules for infectious diseases which are completely neglected, an example being Chagas' disease. The initial budget for this is 50 million US\$, received mainly from donations. Of course, the DNDi is seeking more money, but if eight molecules each costing 500 million US\$ are required, this clearly is an impossible task. The main objective, therefore, is to determine how to develop drugs at lower cost, whilst maintaining the same level of safety. It seems strange that the public's generosity should be mispent on processes of unproven usefulness.

7.6

Future Strategies

What, then, might be the answer to this problem? What strategies should be followed? The first stage would be a scientific cost-benefit analysis of regulatory standards, and this should be strongly promoted. In addition, the local structures should be strengthened and bottom-up approaches built (Figure 7.2), as is the case for the international network of the Pasteur Institute. The Institute is an historical legacy of Louis Pasteur himself, with several institutes having been introduced at the end of the nineteenth century and located worldwide. Strikingly, whilst only 21 institutes were in existence four years ago, the current number is 29 (Figure 7.3). Requests are made throughout the world to share problems of public health, and this is carried out using a bottom-line approach in which it is important to perceive problems and integrate them from the ground up, rather than the other way round. An example taken from the network illustrates that the issues under discussion are not theoretical. Traditionally, the Pasteur Institute in Cambodia vaccinates freely against rabies, as the condition there is widespread among infected dogs. Each year, the Institute receives some 12 000 people who have been bitten by dogs. The vaccine used was originally produced by the Pasteur Institute in Vietnam, using a very old method that employed mouse brain.

- Promote a scientific cost-benefit analysis of regulatory standards
- Strengthen local structures and build bottom-up approaches
- Support innovative partnerships
- Raise awareness and generosity

Figure 7.2 Strategies that should be followed.

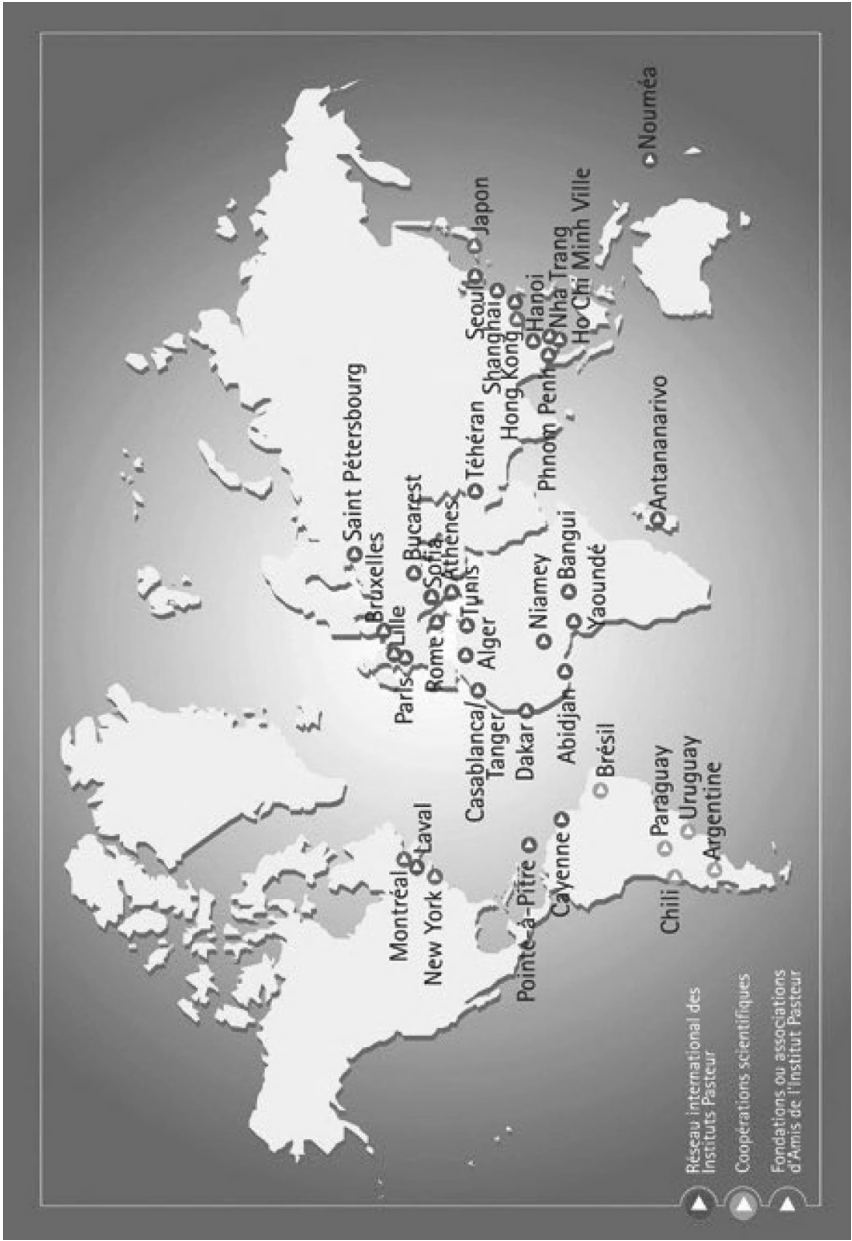


Figure 7.3 Worldwide locations of the Institut Pasteur in 2005.

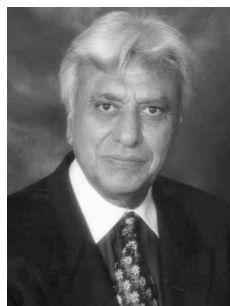
The WHO has, perfectly correctly, recommended that this procedure be stopped, but the new vaccine, which is made on Vero cells, costs five- to ten-fold more than the original. The Pasteur Institute in Cambodia could not afford to buy the vaccine, and so the vaccination rate has plunged. There had been no accidents with the previous vaccine, but the WHO recommendation was clearly correct. Fortunately, friendship and good relations with the industry led to vaccine donations and a transient solution of the problem. Nonetheless, this is typical of the difficulties faced in practice.

Among health initiatives, the GAVI performs an excellent role, while other partnerships such as DNDi, the Medicine For Malaria Venture, and the Global Alliance for Tuberculosis each also deserve support. It is important also to raise awareness and generosity. Awareness means returning to the facts and numbers (as unpleasant as they may be), and accepting the questions. For example, in the United States, a major effort has been made to develop a new vaccine against bioterrorist-transmitted smallpox. In this case, emergency procedures for regulatory processes and development were used to accelerate vaccine production. Why this has not been considered for AIDS, which is an enormous problem? In France, on the other hand, live vaccines are considered as genetically modified organisms (GMOs), with special regulations for their handling having been introduced, for environmental reasons. Sadly, one vaccine candidate was kept in cold storage for a year because the committee involved with the vaccine's environmental aspects took that time to realize that it did not pose any such problem.

Perhaps the question should be asked again – what is the trade-off between principles and people? These are practical issues which must be considered in order to develop the theoretical thinking that supports the action taken.

Author Biography

Hoosen Mohamed Coovadia



Victor Daitz Chair in HIV/AIDS Research, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal (South Africa)

Hoosen Mohamed (Jerry) Coovadia has distinguished himself over many years as a leading paediatric immunologist, a leader in the struggle for a democratic South Africa, a national and international figure in the paediatric world and, more recently, a world authority in the field of paediatric HIV/AIDS, both as a researcher and as a powerful force in shaping policy with respect to the disease.

He specialised in paediatrics at the University of Natal and became a Fellow of the College of Paediatricians of the College of Medicine of South Africa in 1971. In 1974, he obtained his MSc in Immunology from the University of Birmingham. Returning to South Africa after his studies in the UK, he rejoined the Department of Paediatrics at the University of Natal and began to work on the immunology of measles in children. His research in that field led to the award of an MD in 1978, the year in which he was appointed Principal Paediatrician and Senior Lecturer. In 1982 he was appointed Associate Professor and in 1986 Ad Hominem Professor. In 1990, he became Professor and Head of Paediatrics and Child Health at the University of Natal, until the end of 2000. During that time, he created a strong and vibrant department held in high regard for its teaching, clinical excellence and research.

After retiring from this position, H. M. Coovadia was appointed the Victor Daitz Chair in HIV/AIDS Research, and Director of Biomedical Science at the Centre for HIV/AIDS Networking at the Nelson R. Mandela School of Medicine, University of Natal.

His interest in paediatric HIV/AIDS developed in the early 1990s as the extent of the tragedy in South Africa began to be recognised. His particular interest has the transmission of the virus from mother to child. Over the years he has attracted numerous large research grants from both local and overseas donors

and has built up a powerful research team at the Nelson R. Mandela School of Medicine.

H. M. Coovadia, with his research group, has published a number of ground breaking research articles. They were first to suggest that, contrary to received opinion, transmission of HIV from mother-to-child via breast feeding might be substantially reduced if the mother exclusively breastfeeds. While research in this area is not conclusive, if the theory is confirmed it will have significant impact on the health of mothers and children, particularly in developing countries, where formula feeding carries great dangers.

He was appointed by the National Department of Health as Chairperson of the National Advisory Group on the HIV/AIDS and STD Programme from 1995 to 1997, while his international stature in the area of HIV/AIDS led to his election as Chairperson of the XIIIth International Conference on AIDS, held in Durban in July 2000.

Among the other national leadership positions held by H. M. Coovadia over the years are those of Deputy Chairperson of the Transitional National Development Trust of South Africa, Trustee of Independent Development Trust, Chairperson of the Commission on Maternal and Child Health Policy set up by the government in 1994. He is also a founder member of the South African Academy of Sciences.

His research output is prodigious – he has authored or co-authored more than 200 articles in peer reviewed journals, many of them leading international journals. He is co-editor of the textbook *Paediatrics and Child Health*, which is widely used by medical students and junior doctors throughout South Africa.

H. M. Coovadia has received numerous accolades and awards. He was elected a Fellow of the University of Natal in 1995 and was awarded an honorary DSc by the University of Durban Westville in 1996. In 1999 President Nelson R. Mandela honoured him with the Star of South Africa for his contribution to democracy and health and he received a silver medal from the Medical Research Council for excellence in research. In 2000 he received the International Association of Physicians in AIDS and Care Award, the Heroes in Medicine Award in Toronto, Canada, the Nelson Mandela Award for Health and Human Rights and he was elected a Foreign Member of the Institute of Medicine of the National Academy of Sciences.

8

Does Biotechnology Serve Africa's Needs?

Hoosen Mohamed Coovadia

8.1

Introduction

AIDS lends itself to a sense of melodrama, and endless statistics of doom. South Africa has the largest number of HIV/AIDS cases worldwide, and its society – which ironically, when the condition first arose, was just beginning to enjoy freedom – has been devastated by this epidemic. The condition reflects, in its most acute and stark forms, some of the social, economic and political disasters that face the African nations, and in particular those which are currently dealing with this HIV epidemic. The lessons learned are not only biological and medical – many are also political, economical, or social.

HIV/AIDS is a disease like no other, and technology is absolutely critical in the fight against this condition. In the past, many technological disasters have befallen Africa, perhaps most notably the disastrous dumping of formula milk. Africa has a huge backlog to catch up, and there are serious measures to try to overcome some of the problems of what appears to be a benighted continent – the problems of governance, of corruption, and of endless wars. Although not finalized, moves are afoot to persuade black governments to become accountable to some authorities. Today, in Johannesburg, there is an institution called the “African Union”, and there are a number of institutional maneuvers and efforts at achieving peace. To this end, South Africa is playing a leading role in providing a coherence to Africa, to assist in its development and advancement, that has never previously been attempted. It is fair to suggest that it may well be time for the African continent to begin using biotechnology in a way as never before.

8.2
Biotechnology in Africa

In Africa, available biotechnology is affordable, effective and generally accessible, but is simply not being used. Among the major risk factors for the global burden of disease, malnutrition remains the leading contender (Table 8.1). The need for biotechnology to solve the problem of malnutrition is absolute. It was thought that when freedom and democracy were obtained, then malnutrition would disappear, but this has not been the case. In fact, the situation has worsened, mainly because of the AIDS crisis. It is quite clear that there is a need for both agricultural improvements and biotechnology to provide the economic growth that will solve the problems of malnutrition. Indeed, malnutrition is clearly dependent on the input of biotechnology.

Other risk factors for disease include tobacco smoking, physical inactivity and alcohol intake, and most of these have been well-recognized for decades. In the case of tobacco smoking it has taken about 20 years to re-educate people and to change their smoking habits. However, attempting to alter people's sexual activity as a means of halting the advance of AIDS is much more personal, and any re-education must be carried out with a great deal of sensitivity and persuasion.

The data in Figure 8.1 support the point that has already been made. It is known that there are biotechnologies available which work, and are affordable, and it is also known that the absence of these biotechnologies are a major

Table 8.1 Risk factors and the attributable global burden of disease and injury.
(Source: Murray and Lopez, Science 274, 1593–1594, 1996).

<i>Risk factor</i>	<i>Percentage of total deaths</i>	<i>Percentage of total disability adjusted life years (DALY)</i>
Malnutrition	11.7	15.9
Tobacco	6.0	2.6
Hypertension	5.8	1.4
Poor water supply, sanitation and hygiene	5.3	6.8
Physical inactivity	3.9	1.0
Unsafe sex	2.2	3.5
Occupation	2.2	2.7
Alcohol	1.5	3.5
Air pollution	1.1	0.5
Illicit drugs	0.2	0.6

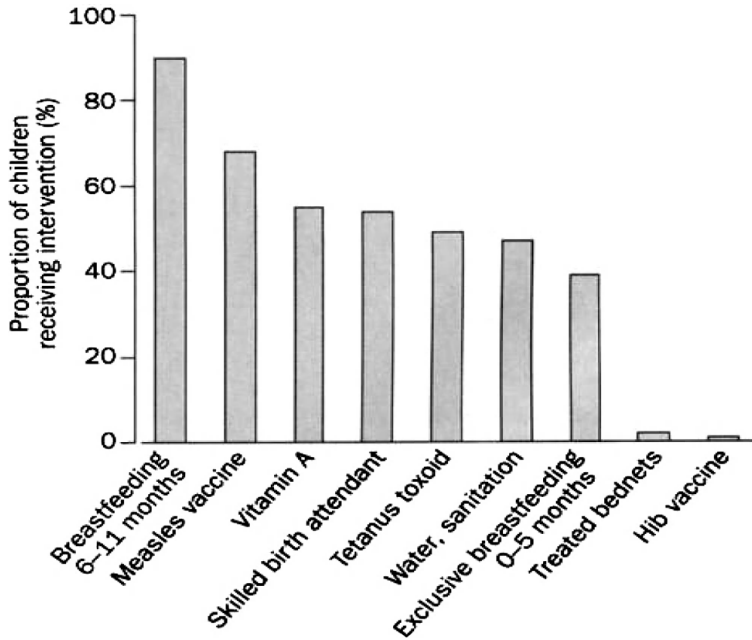


Figure 8.1 Estimated proportion of children aged less than 5 years who receive survival interventions.
(Data are for 42 countries accounting for 90% of all deaths of children aged ≤ 5 years in the year 2000. Source: Bryce et al., *Lancet* 362, 159–164, 2003).

cause of mortality in children aged under 5 years. In fact, the under 5-year mortality rate represents one of the best indicators of child health, and of the health services of the country as a whole. Few of the interventions shown in the figure are either unavailable, prohibitively expensive, or unavailable to every child in every developing country, including breastfeeding, measles vaccines and vitamin A intake. For vitamin A, recent reports from the United Kingdom and Nepal have referred to the use of multivitamins to reduce low birth weight. Other reports from Tanzania have shown that simple multivitamin preparations, when given to women during pregnancy and after delivery, can improve reproductive health outcome. Overall, these are simple technologies, and include simple facilities such as skilled birth attendants, tetanus toxoid, water and sanitation, exclusive breastfeeding, treated bed nets and hepatitis B (Hib) vaccine.

Not all of these major interventions require biotechnology, however. Research into any of these issues is very expensive; for example, one study to examine a hypothesis concerning a link between exclusive breastfeeding and HIV has, to date, cost almost 1 million US\$. These problems appear simple, but the research and technology involved to solve them is very expensive.

Nonetheless, a recent Institute of Medicine report suggested that one of the simplest, most affordable and most essential technologies (if it can be called that) to reduce neonatal mortality is a skilled birth attendant!

Another recent report has suggested that perinatal or neonatal mortality is the single biggest cause of death among children aged less than 5 years. More importantly, three million of the four million deaths involved could be prevented by the use of simple technologies, such as pre-conceptual folic acid. During pregnancy, these technologies would include syphilis testing, tetanus toxoid, or the treatment of asymptomatic bacteriuria. Ironically, the only expensive component that would increase infant survival to any great degree is that of clinical care of the baby when delivered.

It is impossible to speak for the whole of Africa, because it is such a heterogeneous continent. It has heterogeneous HIV infection rates, it has different behaviors, and it has different rates of sexually transmitted diseases (STDs). However, it is clear that there are very few biotechnology companies in Africa as a whole, and the large majority of these – about 100 in total – are located in South Africa (Table 8.2), though only 47 of these were “core” biotech companies.

One interesting point is that of information technology availability in Africa. With regard to Internet usage, as a continent Africa uses only 1% of worldwide Internet technology, and about 80% of that 1% is in South Africa. There is, therefore, a huge gap to be filled. Clearly, the Internet is another technology which is required, is affordable, and is essential, but is not yet available in Africa.

Table 8.2 Biotechnology resources in the US and in South Africa.
(Source: Motari et al., *Nature Biotechnol.* 22, DC37–41, 2004).

Country	Biotechnology resources
USA	No. of public biotech companies: 300 Market capitalization: US\$ 353 billion Annual turnover: US\$ 22 billion
South Africa	No. of biotech companies: 106 (of which 47 are “core” biotech)

8.3

The March of AIDS

Many of today's problems in most African countries have arisen as a result of the AIDS epidemic. This is a devastating disease which affects almost every aspect of society. From an economic standpoint, AIDS causes so much sickness among workers that the economy is failing, and this is having a huge impact on the corporate sector. It is vital, therefore, that antiretroviral drugs are provided urgently, and in many respects it seems that South Africa, as a wealthy country, can afford to do this. Working together, the economists and demographers should be able to provide an essential service to help deal with this epidemic.

Despite these suggestions, it is clear that AIDS has proven to be a dreadful epidemic, and not without effect on the government of South Africa. Since the mid-1990s, the scientific community of South Africa has passed through an absolutely excoriating period, there being wide gulfs between what was scientific truth, what was the government's opinion, and what was everyone else's opinion. It has been proposed that, in this world, there is a "democratization of knowledge" – as if every point of view has equal importance. In other words, truth (or something thought to be the truth) can be established scientifically at high financial cost and effort, only to be nullified by the opinion of a politician or the history of tradition.

People entrapped in the HIV epidemic, and without access to antiretroviral therapy, will seek help in whatever way they can. By this stage they are so desperate that they will accept all of these so-called nonscientific parallel medicines that in time will ruin their lives. But this is simply a measure of their desperation, and it is dreadfully wrong.

The point to be made here is that the government of South Africa has played a peculiar role in denying the existence of HIV/AIDS, with the so-called "panel of experts" being drawn mainly from the United States or from European countries where the condition, although problematic, is far less of a national concern (Table 8.3). It appears that the South African government allowed this situation to develop and has continually undermined scientific efforts to deal with the HIV/AIDS epidemic. Since early 1997, the country has been immersed in a series of exaggerated claims for the drug treatment of AIDS. An example of this was virodene; this was developed in South Africa and considered to be effective against AIDS, but the claims made for its success were found to be totally false. Subsequently, nevirapine – which has saved many thousands of children from being infected with AIDS – was later labeled as a poison or toxin. Dangers were broadcast relating to false evidence having been derived from these studies, and claims were made of American imperialism using Africans as "guinea pigs", but this simply was not true.

Table 8.3 Political evolution of AIDS in South Africa.

<i>Year</i>	<i>Event</i>
1996	Sarafina II play performed
1997	Virodene used in AIDS treatment Advisory Committee established
1998	Medical Control Council founded
1999	Zidovudine treatment available Mother-to-child transmission control taken up
2000	“Panel of Experts” established National AIDS Council founded
2001	Mortality data
2002	Global Fund created

The AIDS epidemic and the difficulties associated with it have affected not only the sickness, health and commerce of the people – it has also perverted the democracy of the country and the peoples’ freedom because they cannot contradict the authorities. South Africa is a genuine democracy, with multiple foci of power, with scientists who are genuinely fearless to state their cases, and an excellent judiciary system. It would seem that South African society is capable of dealing with such a situation, even if it is unusual. Currently, the money needed to care and treat HIV/AIDS each year in Africa is about 9 billion US\$, and this is what the Global Fund aims to achieve (Figure 8.2).

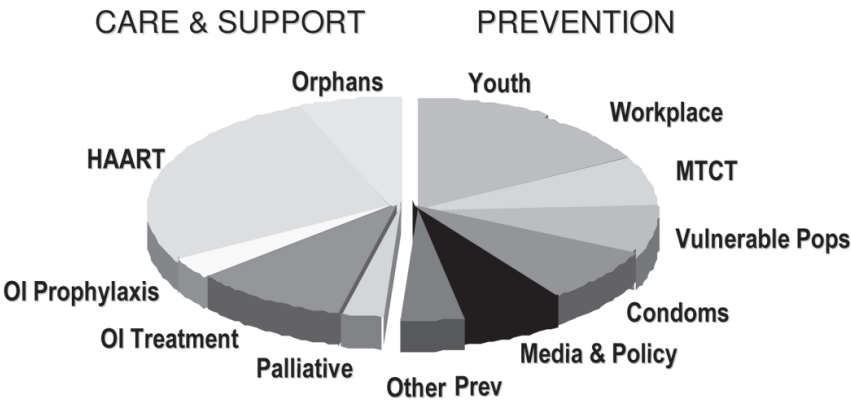


Figure 8.2 Distribution of resources needed for AIDS prevention, care and support. Total funds needed: 9.2 billion US\$.

However, these problems simply cannot be dealt with in the absence of an appropriate technology, appropriate drugs, appropriate community mobilizations, and appropriate international collaborations. Indeed, one of the most gratifying issues concerning HIV/AIDS is the large number of organizations that have joined in this task, including the Global Fund, the World Bank fund, and PEPFA funds and the Clinton Foundation's efforts to provide drugs at reduced prices.

In the Kwazulu-Natal province alone, which has a population of about eight million people, the number of international agencies present is almost uncountable. However, nobody seems to know what these people are doing; they may be working at cross-purposes or even repeating each others' investigations, but there appears to be no correspondence between them. But whatever mistakes they are making, the overall cost each year is 9 billion US\$. This is a huge amount of money – indeed, it is an amount that most countries in Africa could not afford, except perhaps for South Africa.

8.4

Antiretroviral Drugs

The future approach is much more refined, and antiretroviral treatment will be attempted by using the new “3 by 5” initiative (Figure 8.3). Although this scheme is designed to cover three million people, the need is probably for about 9 to 10 million people. There is, therefore, an enormous cost in terms of human resources, human effort, government commitment and all such other resources required to overcome these gaps. The unfortunate point here is that the percentage of people who need antiretrovirals but who actually receive them is pitifully small (Table 8.4).

The introduction of antiretrovirals into the African nations is critical, and fills the medical community with some trepidation. The situation is less bleak for other conditions; for example, when the Hib vaccine was released, the evidence for its efficacy was so good that it could not be ignored. Likewise, for the pneumococcal conjugate vaccines the evidence was absolutely convincing, with benefits not only of pneumonia reduction but also for child health in general. When recommending antiretrovirals, however, the future is much less secure, and what might happen in another ten years' time is far from clear. The scale of the problem is simply so huge that is extremely difficult to predict what might happen to the country's health services, economy, budgets, and health resources. The reason for such complexity is that AIDS requires the re-training of health workers on a scale never seen before. Likewise, from the patients' angle, it takes only a few hours to treat a child with chronic renal failure, but for a child with AIDS the timescale is simply stupefying. In a province of eight million people, 35% of the women are HIV-infected, which

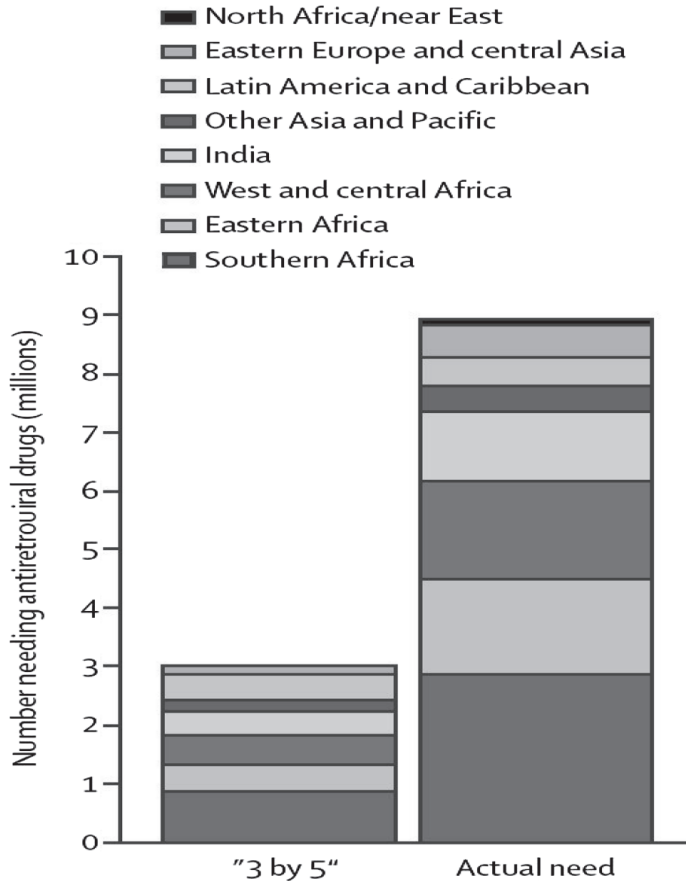


Figure 8.3 Comparison of WHO's "3 by 5" target (set for 2005) and the actual global need for antiretroviral therapy. (Source: Anema et al., *Lancet* 364, 1034–1035, 2004).

in turn infers that one in three women who attend antenatal clinic would be infected. That represents a total of 1.8 million people – a simply phenomenal number. It is inconceivable how drugs can possibly be obtained on such a scale; moreover, the physicians are unfamiliar with the situation and need to be trained. Africa has never had these drugs, and so a supply line must be developed, although if that were to be broken – perhaps if resistance to a drug were to be developed – the situation would rapidly become catastrophic. A short-term break in supply for most health materials is merely problematic, but if antiretroviral supplies were to cease for two months then the problem would be virtually insurmountable.

The possible answer to this problem is that systems must be devised and medical and laboratory staff trained. Procedures which are routine in Europe

Table 8.4 Estimated antiretroviral therapy coverage and overall therapy needs in developing countries. (Source: WHO).

<i>WHO region</i>	<i>Estimated number of people on antiretroviral therapy, June 2004</i>	<i>Estimated antiretroviral therapy need, 2004–2005</i>	<i>Antiretroviral therapy coverage</i>
African Region	150 000	3 840 000	4%
Region of the Americas	220 000	410 000	54%
European Region	11 000	120 000	9%
Eastern Mediterranean Region	4 000	100 000	4%
South-East Asia Region	40 000	860 000	5%
Western Pacific Region	15 000	170 000	9%
Total	440 000	5 500 000	8%

and the United States, such as CD4 cell counts and viral loads are simply unaffordable in Africa. Nonetheless, there is a multitude of issues to put in place for antiretroviral supply, and South Africa has the infrastructure to achieve this. The medical personnel are present and could probably cope with the situation, but the main problem is one of scale.

Whilst it can be assumed that the laboratories are prepared correctly and that the potential problems of resistance can be overcome, a recent report has suggested that in Africa, over the next ten years, even the provision of antiretrovirals will not necessarily reduce the horizontal transmission of AIDS. Such doubt is based on three pieces of evidence, all of which are as yet unproven. There is an expectation that the incidence of AIDS will suddenly fall, although this is uncertain and most likely will not be noticed for the next ten years. It is also suggested that, during a course of treatment there is a 5% incidence of acquired resistance, and that transmission resistance (resistant viruses being transmitted from one person to the next) will be a problem. There is, therefore a clear need to set up public awareness systems, rather than to investigate the transmission of HIV that is resistant to antiretrovirals, and to improve the systems of care such that patients can be managed more scientifically. There is, in fact, an entire list of problems dealing with the implementation of antiretrovirals, the best approach being to develop a worldwide collaboration that will include adequate resources to provide antiretrovirals, yet not compromise preventive activities, which must clearly be continued.

Preventive activities, such as condom use and changes in sexual behavior, are not especially easy to develop, but are generally inexpensive to implement.

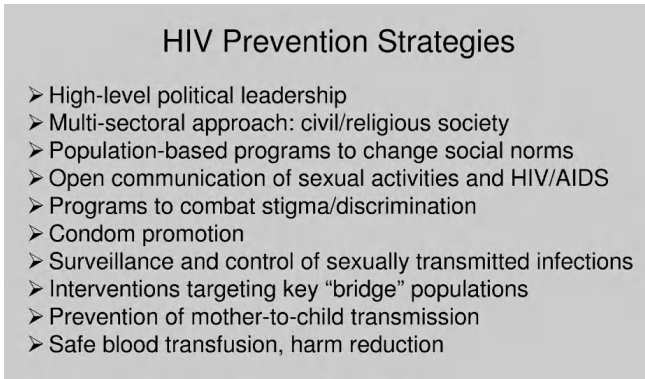


Figure 8.4 HIV prevention strategies.

Today, it is unclear which of these procedures is the most important, and the situation is far from being resolved (Figure 8.4). Many different groups, including religious sects, government ministers, scientists and various communities, have different points of view as to why some success has been achieved. There is clearly a conglomeration of these opinions, but there is no single reductionist approach to solving the AIDS problem.

8.5

Is Biotechnology Succeeding in Africa?

The question remains as to whether biotechnology has served Africa's needs. In the past, this has been thought not to be the case, and the problem with the AIDS epidemic was considered as being largely due to the failure of access to antiretrovirals, with both governments and international agencies as the responsible parties. There is, however, a new effort being undertaken to provide the support needed, notably in the case of the AIDS epidemic which is simply overwhelming parts of Africa. Another – sadly, correct – accusation is that AIDS is diverting funds from all other health aspects, such as breastfeeding and vitamin A intake, for which almost no funds are available because it is so easy to obtain money to investigate HIV. The problem is then that a balance must be found for future investigations, although the future of Africa is clearly dependent upon technology to which Africa's people require increased access. They must be supported in making choices about what they do or do not want, and they need help in order to sustain whatever funding they obtain for the growth and development of those communities. There is particular concern about external funding, which may not be sustainable. However, it is likely that this scale of support is unprecedented, and the opportunity must not be missed.

Even the greatest technology in the world will not be able to solve certain major problems, and indeed Africa has major problems that impact upon the country and its peoples, and also on much of the developing world. Whilst popular concern suggests that modern global power relationships do not affect Africa, the reverse is in fact true. These relationships have fundamental effects, and Africa is itself demanding equal representation on the Security Council of the United Nations. Debate must also be ongoing with regard to the World Trade Organization and intellectual property. Since the 13th AIDS Conference, which was held in Durban, there has been an enormous – and successful – struggle to obtain access to antiretroviral drugs, mainly by pressurizing pharmaceutical companies, businesses and governments. In recent years, the cost of antiretrovirals has plummeted, with typical annual costs in the US of 20 000 US\$ falling to only about 300 US\$ in South Africa. This is indeed an affordable proposition. In the case of nevirapine, the pharmaceutical company has virtually provided it free of charge to poor countries. However, the cost of preventing mother-to-child transmission has moved beyond the area of drug access such that is now a question of costs for staff, infrastructure and antenatal care.

There could be no simpler and cheaper means of reducing mother-to-child transmission of AIDS than single-dose nevirapine. It is easier to administer than polio vaccine (oral tablets for the mother; oral doses for the baby), yet globally less than 20% of those women who require nevirapine actually have access to the drug. In South Africa – which is far wealthier – this figure may reach 50%. Such a situation can only be described as scandalous.

8.6 Conclusions

Today, in Africa, the battle to obtain cheaper drugs and to retain intellectual property rights forms part of daily life. The most awkward aspect of the battle is that it is being fought not against enemies but against friends, through the courts, by using democratic processes to provide antiretroviral drugs and better health services in general. These debates are important, but then so too is the culpability of African countries, the leaders of which, whilst disagreeing violently about many scientific issues, have done much to overcome the problems of conflicts, wars and forced and internal migrations. Technology cannot function in the presence of an unstable society, and good government is essential in order to promote the democracy and freedom that allows not only those in power but also the international community to be questioned on behalf of the people.

Author Biography

Peter Paradiso



Vice President, New Business Development, Wyeth

Peter R. Paradiso, Ph.D., is Vice President, New Business and Scientific Affairs for Wyeth Vaccines, a Division of Wyeth Pharmaceuticals in Collegeville, PA. In this position, he is responsible for global scientific affairs and strategic planning within the vaccine research and development group and for commercial oversight of products in development. He has worked in the field of vaccine development at Wyeth for the past 20 years. P. R. Paradiso served as a member of the National Vaccine Advisory Committee (NVAC) and is currently a member of the Advisory Council on Immunization for New York State and a liaison member of the CDC's Advisory Committee on Immunization Practices (ACIP). He has published broadly in the field of pediatric vaccines, especially in the areas of glycoconjugates, combination vaccines and respiratory viral vaccines. P. R. Paradiso has been involved in the development and the global registration of vaccines for H. influenzae type b, rotavirus, Neisseria meningitis group C, Streptococcus pneumoniae and influenza. He has also served as an advisor to the WHO's Strategic Advisory Group of Experts on vaccines and to the GAVI Task Force on Research and Development.

9

New Vaccines with Global Impact: The Issue of Access

Peter Paradiso

9.1

Introduction

In this chapter, attention will be focused on the development of new vaccines rather than improving the access to available vaccines, as has been described in some of the previous chapters in this volume.

There are many issues involved, the majority of which are ethical in nature. In general, the vaccine market is one of most difficult to penetrate because experience is limited, and this presents some of the greatest challenges. Some years ago, in a movie called *Field of Dreams*, the main character built a baseball field, following the slogan of “... build it and they will come”. The baseball field was built, and the people did indeed come. Today, this same philosophy is used for some vaccine developments, and this surely is indicative of the confidence expressed in vaccines, and in their market place.

The vaccine market place is an environment of great uncertainty, however – using the analogy with *Field of Dreams* – the question is whether they will come and, if they do, how many, when, and how to build and to prepare for that. In Chapter 7, Philippe Kourilsky referred to the “90–10 gap” as it applied to existing vaccines, as well as to vaccines under development. It is disconcerting to see such a high disease burden for measles when a vaccine has been available for 30 years but has simply not been taken up. When considering what production capacity should be built or considered for new vaccines, and how they should be tested, it is perhaps difficult to see the route ahead because of the unsure delivery mechanisms involved.

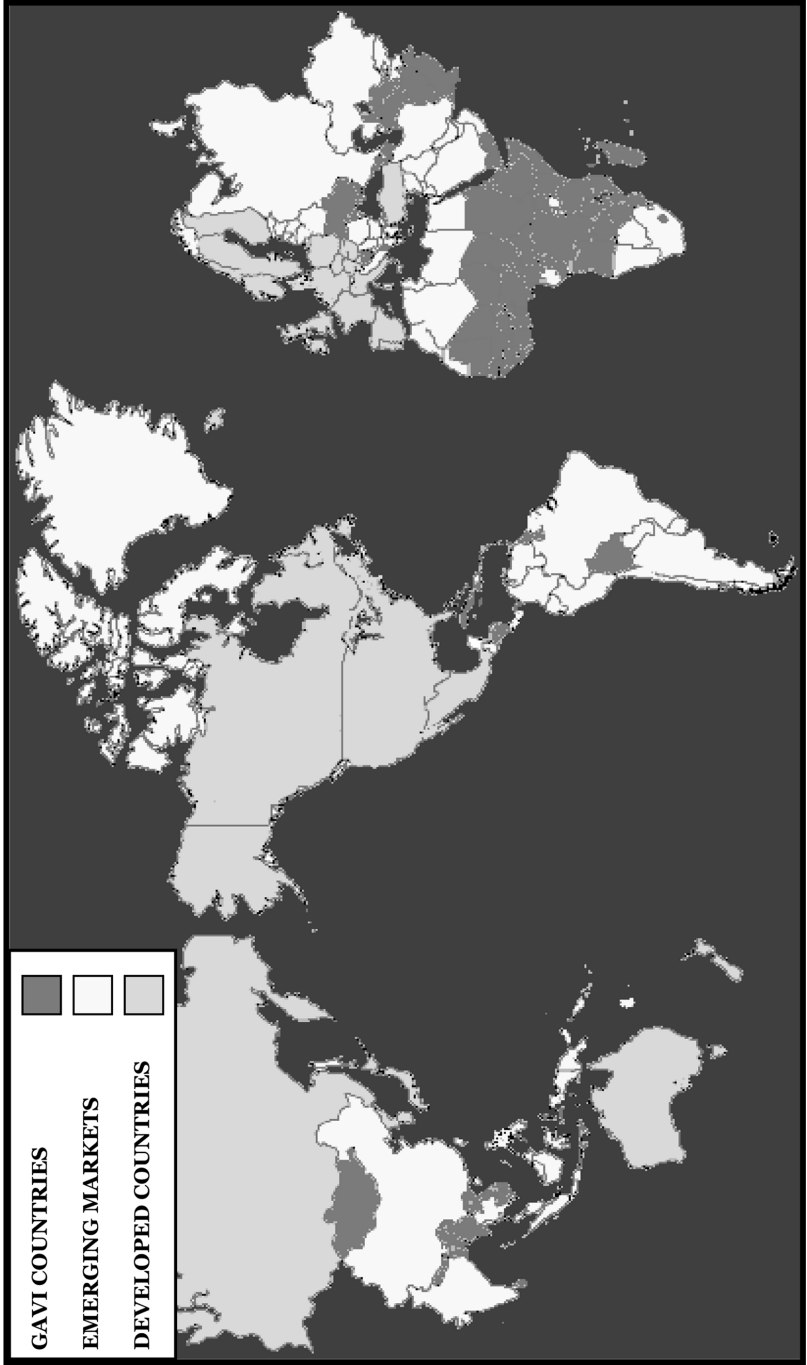


Figure 9.1 Countries covered by the Global Alliance for Vaccines and Immunization (GAVI).

9.2

Vaccine Development

There are two main areas involved in vaccine development. It is clear that issues of impact have been important, whilst establishing value is also important in the development of vaccines and testing of their efficacy. Building awareness, country by country, region by region, is critical in all market places, and again participation is via collaboration, as is the case with epidemiology and vaccine studies. To determine demand and to ensure supply is very difficult within this environment, but these must be undertaken in order to help predict an assurance of delivery systems and infrastructures.

The map in Figure 9.1 highlights the market places for vaccines worldwide. Of the three market places considered, those of the developed countries are where attention has traditionally been focused. Then, there are the emerging markets – these are quite large and have economies somewhere between those of the developing country markets and the United States and Europe. Finally, there are the least developing or poorest countries, with per capita incomes of less than US\$ 1000 per year. The problem here is how to balance demand and production between these market places.

From the perspective of size, the developed and the least-developed markets are quite similar, whilst the less-developed markets are slightly larger, though not by orders of magnitude. So, it sometimes becomes less of an issue of whether the capacity can be built up, but more of understanding how much capacity is needed and what the demand will be.

9.3

Vaccine Supply

There must first of all be a partnership in determining the answers to some of these issues for all of the vaccines under development, and that partnership must include vaccine development and supply. Generally, the manufacturers, the donors and the financiers of those vaccines and the countries must be involved in the access and the delivery. Facilitating that are groups such as the Global Alliance for Vaccines and Immunization (GAVI). Recently, these have become highly effective, and have formed important working teams to focus on specific vaccine areas such as rotavirus, meningococcal disease and pneumococcal disease. The aim of this is to advance vaccine access, because past experience shows that it takes a long time for vaccines to be transferred from developed markets to developing markets. Figure 9.2 shows the situation for two vaccines in low-income countries, from the time of launch onto the developed market. *Haemophilus influenzae* B vaccine was introduced in the late 1980s/early 1990s in the developed world, in the United States and in

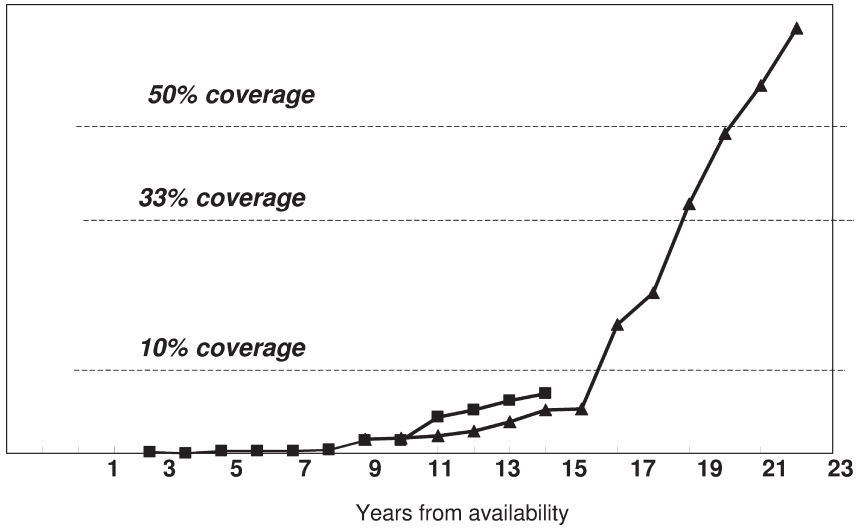


Figure 9.2 Delay in the use of vaccines in low-income countries. Coverage data are for the 75 lowest income countries. ▲ hepatitis B vaccine; ■ *H. influenzae* B vaccine.

Europe. Today, 15 years later, the vaccine still has not been successfully introduced everywhere, despite its value having been recognized. The delivery simply has not happened. The GAVI has stated that their goal is to enhance uptake, so that better access to vaccines is achieved more quickly. However, from the viewpoint of the vaccine manufacturer, it is difficult to identify in which direction the route should progress – where to manufacture the vaccine, at what level, and at what point in time.

9.4 Disease Burden and Vaccine Efficacy

The relationship between disease burden and vaccine efficacy is referred to as “establishing value”, and includes the issue of clinical trials. It also involves where and when such trials are conducted, the ethics involved, and the impact that these trials will have. The accusation is often leveled that clinical trials are not conducted in developing countries simultaneously to their being conducted in developed countries; that our focus is centered on the developed countries because that is where the market places are. However, this is not always true, and trials have been conducted and efforts made to generate data that will be available in a variety of market places. In either case, it does not appear to influence the issue of access.

In recent years, there are three notable vaccines that have been prepared, these being directed respectively against *H. influenzae* B, rotavirus and *Streptococcus pneumoniae* (Table 9.1). *H. influenzae* B is reported to be responsible for 400 000 deaths each year. Rotavirus and *S. pneumoniae* cause serious diseases, but in general, the primary efficacy trials are performed in developed country settings, and in the US and Europe in particular. Subsequently, their value and the implications of clinical trials performed in developing countries, either pre-licensure or post-licensure, becomes an issue of vaccine development. Moreover, there are ethical considerations as to whether this occurs pre-licensure or post-licensure, in addition to certain responsibilities for access after the trials have been completed.

Table 9.1 New vaccines with global impact.

Pathogen	Global health burden [deaths per year]	Vaccine development history
<i>H. influenzae</i> B	400 000	Pre-licensure efficacy trials in US and Finland Licensed for infants in the US and EU (1990) Post-licensure efficacy trial in Chile (1992–1995) Post-licensure efficacy trial in The Gambia (1993–1995)
Rotavirus	440 000	Pre-licensure efficacy trials in the US and Finland Pre-licensure efficacy trials in Venezuela Efficacy trials of prototype vaccine in Peru and Brazil Licensed in the US (1998) and EU (1999), but withdrawn from market in 1999 Little interest post-withdrawal in developing countries
<i>S. pneumoniae</i>	> 1 000 000	Pre-licensure efficacy trial against IPD in the US Licensed in the US (2000) and EU (2001) Post-licensure efficacy trial against IPD and pneumonia in South Africa and The Gambia

IPD = invasive pneumococcal disease.

9.4.1

Haemophilus influenzae B

The *H. influenzae* B vaccine was licensed in the US and in Europe in infants in 1990, and efficacy trials were conducted predominantly in the US and in Finland. The efficacy was found to be very high for these vaccines, and approached 100% in many cases. In vaccinology terms, *H. influenzae* B has a saccharide on its outer shell against which an antibody can be induced. When this occurs, the bacterium is killed and the vaccine will be effective. The clinical trial showed this suggestion to be true. The next step was that if an antibody to the saccharide could be induced in a population, then the vaccine could be confidently expected to be effective. However, the issue is then whether it is ethical to continue with placebo-controlled trials when the vaccine's efficacy is virtually certain. There are both pros and cons to this approach, and in many cases it is questionable. It came as no surprise when, in subsequent randomized trials in Chile, the *Haemophilus* conjugate vaccine demonstrated the same level of efficacy. A subsequent trial in The Gambia showed vaccine efficacy against invasive disease. This was an example of a trial being conducted in a developing country and at the same time adding to the knowledge base, because surprisingly there was seen to be a significant reduction in all-cause pneumonia from *H. influenzae* B – a benefit which had not previously been shown.

If conducting a clinical trial in a developing country can add to the current information base, then the trial's outcome can be deemed valuable. However, the outcome with *H. influenzae* B had not been anticipated, so the prediction of a vaccine's value may be difficult. When, in general, the tenet is that "more information is better", the ethics of conducting trials in developing countries become slightly blurred when important new findings sometimes result from these.

9.4.2

Rotavirus

With RotaShield, the quadrivalent rotavirus vaccine that was licensed in the US during the late 1990s, pivotal trials were performed again in the US and Finland. There is in fact a pattern here, that Finland and the US seem to be excellent locations for efficacy trials! Equivalent vaccine efficacy pre-licensure trials were performed in Caracas, Venezuela within a developing country setting, whilst efficacy trials of prototype vaccines prior to RotaShield release were conducted in Peru and Brazil. Many of the trial outcomes were similar, with RotaShield showing very significant efficacy against severe disease. Thus, at the time of licensure in the US and in Europe, there was a robust efficacy profile for this vaccine in a variety of environments in both developed and

developing country settings. The experience at the time of licensure, when communicating with health communities in Asia and Africa, was that further trials were required and that these should be conducted in the communities' regions. In Asia and Africa there was dissatisfaction at the level of efficacy, despite the manufacturers having embarked on Phase I (safety and immunogenicity) and Phase III (efficacy) trials before RotaShield could be introduced into developing countries. Thus, despite having conducted pre-licensure trials in a setting that was comparable to that in many developing countries, the vaccine was deemed unacceptable for these countries. In the US, there was also an issue with intussusception, an adverse event that occurred in about 1 in 10 000 patients, and consequently the recommendations for vaccine use were withdrawn. The clinical trials were first put on hold and then halted by the regulatory agencies. The message was clear – if there is a safety issue that leads the US and Europe to reject use of the vaccine, it will not be acceptable for developing countries, even if there is a fundamentally different risk/benefit ratio in these countries. Following the safety profile problems of intussusception, there was minimal interest in this vaccine and so it was not marketed, regardless of its potential benefit.

9.4.3

Streptococcus pneumoniae

The most recent experience was with *Streptococcus pneumoniae*. A seven-valent conjugate vaccine (Prevnar) was licensed in the US in 2000 and in Europe in 2001, and showed very high efficacy against invasive pneumococcal disease. As with the *Haemophilus* vaccine and meningococcal conjugate vaccines, this efficacy was correlated with an ability to induce an antibody response to the saccharides of the conjugate. During the course of the development, efficacy trials were initiated in several developing countries, including South Africa and The Gambia. These trials spanned the licensure period and, on completion, demonstrated efficacy not only against invasive disease but also – importantly – against pneumonia. Again, this is an example of efficacy trials that had a different endpoint which was focused on the needs of the population, in order to establish value among the population where the trial was conducted. In the US, the primary concern was invasive disease in meningitis, whereas in Africa the major concern was pneumonia. These were the endpoints of the trial. The vaccine was a nine-valent conjugate; it had the seven types that were in Prevnar, plus types 1 and 5 that are prevalent in Africa. The most important point of the trial was to determine whether, when serotypes were added, the efficacy remained. The trial would also confirm whether the vaccine was effective in the setting of urban Africa and under the EPI schedule. The endpoints were invasive disease, all X-ray proven pneumonia, admissions to hospital for any cause, and death from any cause. The results were quite

Table 9.2 The Gambia pneumococcal vaccine trial.
The vaccine used in this trial was a 9-valent conjugate vaccine.

<i>Endpoint</i>	<i>Efficacy [% reduction]</i>
Invasive disease	77 ^{a)}
X-ray-positive pneumonia	37 ^{a)}
Hospital admission	15 ^{a)}
Death	16 ^{a)}

^{a)} Statistically significant reduction.

outstanding, with a 77% reduction in invasive disease (which perhaps was expected based on other trial outcomes), as well as a reduction in all X-ray confirmed pneumonia of 37%, hospital admissions of 15%, and mortality of 16% (Table 9.2).

9.5 Ethical Perspectives

Two important issues arose from this trial, from an ethical perspective. The first issue was that although mortality was taken as a primary endpoint, during the course of the trial it became clear that many trial operatives were uncomfortable about counting and measuring deaths. Consequently, mortality was used as a secondary endpoint. However, despite doubts related to the power of the trial, it transpired that so many people died as a result of pneumococcal infection, mortality could indeed be used as an endpoint.

The second issue, which was addressed during the middle of the trial, was whether it was ethical to continue with a vaccine that had already been licensed in the US and Europe and was clearly effective. The decision was made to continue the trial, on the basis of the pneumonia endpoints and that new data would be obtained. The question is therefore, if efficacy has been demonstrated in one population, is it ethical to perform further placebo-controlled trials? In many cases the answer to this is yes, but only if fresh data are derived and new information is provided (Figure 9.3). The important point from an ethical perspective is what is required after the trial has been completed.

Two considerations spring to mind. The first concerns the placebo group if the trial is successful: in clinical trials involving efficacy, vaccine is often subsequently offered to the placebo population, and indeed this is often required in the protocol. This is no different from studies conducted within developing countries, although on occasion the method of vaccine delivery presents a

Is it ethical to do further placebo-controlled trials if efficacy of a vaccine has already been demonstrated in one population?

Pre-trial considerations

- Population effects on efficacy may be discovered
- New, perhaps more relevant, endpoints may be studied
- How likely is the population to have access to the vaccine if no trial is conducted?
- Will a trial have a positive impact on the subsequent introduction of the vaccine?

Post-trial requirements

- Vaccinate the placebo population
- Ensure access of the general population to the vaccine

Figure 9.3 Ethical issues associated with clinical trials in developing countries.

major challenge. On completion of the trial, there is also an obligation with regard to providing access to the trial vaccine, or to a vaccine that has already been tested. In a recent report that was posted on the Science and Development Network website (www.scidev.net, October 2003) B. Greenwood and W. P. Hausdorff spoke about post-trial access and what should be required. Their suggestion was that the manufacturers offer to supply the vaccine at a discounted, “affordable price” which reflects the economy of the country or region. The Minister of Health would then decide whether, at an affordable price, the country was interested in utilizing the vaccine and would be willing to take on the responsibility for the community’s health. The third option would be that the Minister of Health was not be willing to make such a contribution, and the venture would be deemed not sufficiently important to proceed.

These points are easy to note down, but are difficult to deal with. The idea of the manufacturer donating vaccines to populations in which clinical trials have been conducted has been considered as a “cop-out”, as it removes the potentially problematic issue of deciding an affordable price, and of deducing a long-term price for developing countries in general. Whether this approach might provide a sustainable mechanism for the country receiving free vaccine is unclear, but – somewhat surprisingly to me – as a company we have consistently been discouraged to do so during these studies.

9.6

Vaccine Demand and Capacity

If clinical trials are conducted successfully within a developing country setting, the next major decisions to be taken are related to adequate vaccine supply and confirmation of an ability to meet the demand generated. There are three market segments to examine, the first of which is to establish an affordable

price. Discussions on price take the form of a circular discussion: How much vaccine is required? What is the cost? How can the cost be deduced until the demand is known? When is the vaccine required? In order to minimize this situation, the GAVI has set up mechanisms to ensure much more direct interaction to predict and understand both demand and timing, and to relate these properties to cost. The subject of cost and building up of capacity can be considered in two ways. The first way is to use existing capacity and to better utilize existing facilities, whilst the second way is to build new capacity. The latter approach represents a much greater challenge because it is associated with the prediction of demand. The difficulty here is that it takes five years to build and license an increased capacity. So, it is vital that the future demand is known, as it would be disastrous for new capacity to be idle due to a lack of demand.

The concept of alternative formulations and presentations for different market places must also be considered. Whereas in developing countries the market is predominantly multidose, in developed countries vaccine administration is invariably single-dose vials, without preservatives. Presentation – which seems so trivial – becomes an entire manufacturing regulatory process that must be traversed in order to develop different formulations for developing countries. In this respect, the manufacture of vaccines with preservatives becomes another issue. It is, therefore, critical to have third-party collaboration, and the partnerships created in developing countries, linked with the capacity build-up there, will probably be vital for the success of the vaccine manufacturers.

9.7

Affordability and Sustainability

It is important to recognize and to determine what is affordable and what is sustainable. It is likely that tiered pricing represents the only route to take, with the least-developed countries paying by far the least amount. This situation must be viewed by companies as being philanthropic – there is no other way to view it. Whether the vaccine is donated or a charge of a few dollars is made is irrelevant; the cost will inevitably be far less than that in a different setting, and may often be many-fold less than the production cost. The fact that such a gesture can be made, and without too much pain, is probably a good enough reason to do it. However, it must be understood by all concerned that to charge less in some markets does not mean that the same price is applicable worldwide.

Access to vaccines requires close collaboration between partners, and it must be emphasized that during the past five years the environment created by the GAVI, with all their effort, has become a very pleasant workplace. Ethical

issues must be addressed by all partners, and the risks to a company's shareholders must be both identified and expressed. Moreover, the philanthropic nature of supply must be acknowledged and the need to tier pricing to match markets must be accepted.

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Key Messages

Author Biographies

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Gerald T. Keusch is Assistant Provost for Global Health, Boston University Medical Campus and Associate Dean for Global Health at Boston University School of Public Health. Prior to this appointment, he served as Director of the Fogarty International Center at the National Institutes of Health and Associate Director for International Research in the office of the NIH Director. A graduate of Columbia College and Harvard Medical School, he is Board Certified in Internal Medicine and Infectious Diseases. He has been involved in clinical medicine, teaching and research for his entire career, most recently as Professor of Medicine at Tufts University School of Medicine and Senior Attending Physician and Chief of the Division of Geographic Medicine and Infectious Diseases, at the New England Medical Center in Boston, MA. His research has ranged from the molecular pathogenesis of tropical infectious diseases to field research in nutrition, immunology, host susceptibility, and the treatment of tropical infectious diseases and HIV/AIDS. He was a Faculty Associate at Harvard Institute for International Development in the Health Office. Dr. Keusch is the author of over 300 original publications, reviews and book chapters, and he is the editor of 8 scientific books. He is the recipient of the Squibb, Finland and Bristol awards for research excellence of the Infectious Diseases Society of America, and has delivered numerous named lectures on topics of science and global health at leading institutions around the world. He is presently involved in international health research and policy with the NIH, the U.S. National Academy of Sciences' Institute of Medicine, the United Nations, and the World Health Organization. Under his leadership, the programs of the Fogarty International Center were greatly expanded and focused on the creation of a global culture of science and to harness science for global

health. Fogarty now supports research, capacity building, and science policy on the pressing global issues in infectious diseases, the growing burden of non-communicable diseases, and critical cross-cutting social science issues such as the ethical conduct of research, intellectual property rights and global public goods, stigma, the impact of improved health on economic development and the effect of economic development on the environment and health.



Kul Chandra Gautam

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Kul Chandra Gautam is currently Assistant Secretary-General of the United Nations and Deputy Executive Director of the United Nations Children's Fund (UNICEF) at its Headquarters in New York. He is responsible for providing leadership in strategic planning, programme development, resource mobilization, and promoting partnership for children and development among UN agencies, donors and civil society organizations.

Mr. Gautam has had a long and distinguished career with UNICEF. Starting in 1973, he served as Programme Officer in Cambodia and Indonesia, as UNICEF Country Representative in Laos, Haiti, and India, and as Regional Director for Asia and Pacific. He also served as Chief for Latin America and the Caribbean, as Director for Planning, and Director of Programme Division at UNICEF Headquarters in New York.

As Director of Programme Division and Acting Deputy Executive Director (Programme), Mr. Gautam had major responsibility for developing and overseeing policy and programme strategies for UNICEF cooperation in developing countries in the early 1990s.

He was the key senior UNICEF officer responsible for drafting the Declaration and Plan of Action of the 1990 World Summit for Children, the largest gathering of world leaders in history until that time. In May 2002 he led the organization of another major United Nations conference, the Special Session of the General Assembly on Children attended by 70 world leaders and thousands of child rights activists and civil society leaders, including celebrities and Nobel Prize Laureates.

Mr. Gautam is a citizen of Nepal. He received his higher education in the United States of America, at Dartmouth College, Princeton University, and Harvard University. Mr. Gautam is married with a daughter and a son.



George R. Siber

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George R. Siber joined Wyeth Lederle Vaccines as Vice President and Chief Scientific Officer in August, 1996. He became Senior Vice President in August, 1999 and Executive Vice President in June, 2002. In this capacity he is responsible for discovery research in bacterial vaccines, viral vaccines, immunology and genetic vaccines, process and analytical development, clinical development, and scientific affairs for Wyeth Vaccines Research.

While at Wyeth Dr. Siber has overseen the development and approval of an acellular pertussis vaccine for infants (Acel-Imune), a vaccine to prevent Rotavirus diarrhea in infants (RotaShield), a glycoconjugate vaccine to prevent group C meningococcal meningitis (Meningitec), a 7 component glycoconjugate vaccine to prevent pneumococcal disease in infants and children (Prevnar), and a cold adapted nasally administered influenza vaccine in collaboration with MedImmune (FluMist).

Prior to joining Wyeth Dr. Siber was Director of the Massachusetts Public Health Biologic Laboratories and Associate Professor of Medicine with the Harvard Medical School, Dana Farber Cancer Institute. During this time he oversaw research on acellular pertussis and Hemophilus influenza vaccines, the development and approval of CMV Immune Globulin (Cytogam®) and RSV Immune Globulin (Respigam®) and the production of DTP vaccines and immune globulins for the State of Massachusetts.

Dr. Siber's research interests have included the evaluation of the human immune response to polysaccharide and protein antigens, the development of vaccines and immune globulins against Hib, pneumococci, meningococci, pertussis and RSV and maternal immunization to prevent perinatal and early neonatal infections. He has authored more than 150 scientific articles in peer-reviewed journals. He holds 3 issued patents which support a licensed diagnostic test for meningitis (Bactigen®) and an antibody based preventative for respiratory syncytial virus infections in high-risk children (Respigam®).

Dr. Siber has served on numerous advisory committees including the WHO/UNDP Steering Committee for Encapsulated Bacterial Vaccines, the Steering Committee for Development of Streptococcus Pneumonia Vaccine for the Pan American Health Organization, the Institute of Medicine Committee on the Children's Vaccine Initiative, the NIH Blue Ribbon Panel for Bioterrorism and its Implications for Biomedical Research, Chairman of the review of the US Army's HIV research program, and the Board of Scientific Counselors for the National Vaccine Center.

Synthesis and Recommendations

Gerald T. Keusch, Kul Chandra Gautam, and George R. Siber

1

Basic Facts

The global situation with regard to vaccines and vaccination can be characterized as follows:

- 75% of children are immunized, but 36 million newborns remain without access to basic vaccines.
- Between 2 and 3 million children will die from a vaccine preventable disease each year. This approximates to 250,000 deaths per month = 1 “Invisible Tsunami” per month.
- In the last 5 years, global action such as the GAVI initiative has reached 45 million more children with new vaccines and prevented 700,000 deaths.
- The Biotechnology revolution opens new avenues for vaccine discovery.
- Vaccines have taken 15–20 years to reach developing countries after their first introduction in developed countries.

2

Key Concerns

Key concerns in the global health sector for vaccine development and vaccination have been identified that must be overcome to improve the current situation.

- The true value of vaccines is not appreciated.
- Infrastructure deficiencies continue to impede access in developing countries.
- Funding is not sustained over time; one reason for this is donor fatigue.

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- There is a lack of political commitment because benefits from vaccination are delayed as compared to other health initiatives.
- Public trust in vaccination is lost.
- Technical challenges remain daunting for high priority vaccines like HIV, tuberculosis and malaria.
- Increasing aversion to risk has led to increasing regulatory barriers and increasing costs of development.

3

Call for Action

Action points have been identified to address the key concerns as given above. Actions needed are different with regard to vaccines already in use (old vaccines), those that are ready to be used (recent vaccines), and those that are at present not available (vaccines to be developed).

3.1

Old Vaccines

These are vaccines that are fully developed, have an established record of safety and efficacy, where supply is abundant, and the price is not the issue. Among this group are vaccines against, e.g., measles, pertussis, tetanus.

- Access is the critical barrier.
- To improve access, multiple partnerships are needed.
- For a vaccination program to be successful, commitment must be maintained by each partner:
 - Local governments must provide infrastructure, staffing and ensure a working cold chain.
 - Global Initiatives like GAVI and the Gates Foundation must provide funding.
 - Vaccine manufacturers must provide adequate vaccine supply, including low-cost generics.

3.2

Recent Vaccines

These are vaccines that have been recently developed. They are available but not used. Among this group are vaccines against, e.g., rotavirus and pneumococcus.

- High price is required to recover development costs and capital expenditure on manufacturing facilities, unless one or more of the following criteria can be met:
 - Advanced purchasing commitments are signed.
 - There is help from an International Financing Facility.
 - Three-tiered pricing is introduced.
- Access needs to be scaled up

3.3

Vaccines to Be Developed

These are vaccines that have not yet been developed, but where a major need exists. Among this group are vaccines against the “big three”, malaria, tuberculosis, and HIV.

- Scientific breakthroughs are needed (compare the Gates Grand Challenges in Global Health).
- Cost of vaccine development must be reduced, e.g. by lowering regulatory barriers.
- Public investment must be increased, e.g. by creating a Global Fund for Tropical Disease.
- Public awareness and acceptance of the required investment must be increased.

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Module I

Agriculture: Livelihood, Politics and Sustainability

Introduction

*Dominique Lecourt**

The application of life sciences to plant culture and cultivation represents an amazing and long-awaited feat of human intelligence. These advances contribute significantly to the abundance and safety of food for the poorest populations. This includes increased nutritional quality in developed countries where the progression of obesity, particularly among young people, is expanding at an alarming rate. Nutritional research established that foods too rich in animal fat carries is correlated to obesity; that the dietary ratio of saturated fat to unsaturated fat affects the risk of arteriosclerosis, and that many foods influence susceptibility to disease, including certain cancers. One can easily envisage a science-based agriculture which would contribute to the fight against these diseases.

Genetic modification of plants and animals undoubtedly constitutes an important stage in the ability of man to control the medium of his own existence. These modifications carry the promise of reducing the intensive use of chemical fertilizers, pesticides, weedkillers and fungicides which are costly to farmers, and which pose a danger to the health of consumers. They also promise to bring countries of the South the ability to cultivate plants whose nutritional value will be increased, including golden rice enriched in vitamin A, which helps to alleviate blindness striking thousands of people due to a deficiency of this vitamin. However, others believe that GMOs pose serious health risks, albeit in the absence of evidence to this effect. One worries in addition about the reduction of biodiversity on a global scale. How can we prevent the farmers of the South from being denied access to improved seeds in order to benefit some large companies sharing the world market? How can we ensure that technological innovations capable of improving their condition does not increase their misery instead?

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1

Agricultural Research to Improve Human Nutrition

Per Pinstrup-Andersen

1.1

Introduction

In this chapter I would like to address three main questions. The first question is how serious is the nutrition problem; the second question relates to how agricultural research and policy can improve nutrition; and the third question is whether nutrition goals should guide agricultural research and policy. The solution to this dilemma may be obvious to nutritionists, but it is less clear to those involved in agriculture and economics. It is important at this point to stress the seriousness of the problem. There is today a triple burden of malnutrition – hunger, hidden hunger (which relates to specific nutrient deficiencies), and overweight and obesity (Table 1.1). So, if people think that nutrition problems involve only the developing countries, it is necessary that the situation be re-considered.

Table 1.1 Global prevalence of malnutrition.

Condition	No. of people affected (millions)
Hunger	800
Child stunting	182
Child underweight	150
Hidden hunger	
Iron deficiency	2000
Vitamin A deficiency	500
Zinc deficiency	2000
Overweight or obesity	1000
Overweight (pre-obese)	700
Obesity	300

Table 1.2 Prevalence of hunger by region.

Region	No. of people affected (in millions)	% of local population	% of global hunger
Asia	508	16	64
South Asia	315	24	39
Sub-Saharan Africa	196	33	25
Other	96	—	11
Total	800	17	100

Although the problem involves both high-income and low-income countries, the difference is that there are two malnutrition-based questions. It is known that about 800 million people suffer from hunger, and about 180 million preschool children are stunted and fail to grow to their full potential. Another 150 million are underweight, with all the associated consequences. Hidden hunger may affect up to two billion people in the case of iron- and zinc-deficiencies, while vitamin A deficiency affects another half-billion. Although these public health problems of malnutrition are very serious, there are in fact more overweight and obese people in the world today than those who suffer from hunger. About one billion people are classified as being either overweight or obese; of these people, two-thirds are overweight without being obese, and the other one-third suffers from obesity (Table 1.2).

Whenever the subject of hunger is raised, it is generally Sub-Saharan Africa that is referred to, because so many hungry people live there. In fact, most of the hungry people in the world live in Asia, but there the trend is heading in the right direction and there are fewer hungry people each day. In Sub-Saharan Africa, however, the trend is in the wrong direction, with increasing numbers of people suffering from hunger every day. It is important to keep this concept in mind because, depending on which problem is to be solved, the focus will be centered on one region or another.

1.2

The Green Revolution

The good news is that, during the past 30 to 40 years, the world has made tremendous progress in reducing hunger and making more food available. As a result, the percentage of the world's population that suffers from hunger has fallen from 37% to about 17%. This amazing accomplishment has been partly masked by the fact that the population has risen, and consequently the absolute number of people who suffer has decreased only marginally (Table 1.3).

Table 1.3 The development of world hunger.

<i>Year</i>	<i>No. of people affected (in millions)</i>	<i>% of global population</i>
1970s	960	37
2005	798	17

One problem here is that the improvements have been very unevenly distributed, with major reductions in the numbers of hungry in East and Southeast Asia, primarily – but not exclusively – in China. There have been some slight increases in South Asia, but most importantly there are more hungry people in Sub-Saharan Africa every day, and the situation is deteriorating. On a global level, there was an improvement during the first half of the 1990s, but this was followed by deterioration such that there were more hungry people in the late 1990s than in the mid-1990s and the initial progress was nullified. Much of this progress is due to a greater availability of food at a lower production cost, and therefore lower prices to the consumers. This trend, of course, is due very much to the research efforts that were started in Asia and later moved to Latin America and Africa – a situation referred to as the “Green Revolution”. Although the Green Revolution was the most successful development effort ever seen, it did not solve all of the problems – indeed, it created some new ones. Nonetheless, millions of people who were predicted to die from starvation in Asia during the 1960s and 1970s were saved. So, when the subject of pesticide and fertilizer use is mentioned, these points must be kept in proportion. Whilst today we can begin to reduce the use of agrochemicals now that there is more food available, in the 1970s the problem was to produce more food at lower unit cost, so that it could be made available to poor people.

And the whole scheme was a tremendous success. During the past 40 years, the amount of food available per person – in daily calories – has increased from about 2000 to 2700. This represented a vast improvement, as not only were the needs of an increased population met, but the per capita consumption was also increased.

1.3

The World Food Goals

In 1996, 180 countries met at the World Food Summit (WFS) and agreed on a goal to reduce by half the number of hungry people between 1990 and 2015 (Figure 1.1). It can be seen from these data that, in 10 years’ time, there will be approximately the same number of hungry people as exist today. Clearly,

the goal is not being met. The majority of the progress during the 1990s was made by China; hence, if China were to be removed from the equation there would be a dramatic increase in the number of hungry people, despite all of the world's governments having agreed to follow the WFS goal. It can be argued that those who make the promises do not fulfill them, and the situation is especially bad in Sub-Saharan Africa, in West Asia, and in North Africa. Figure 1.1C indicates the number of hungry people only from Sub-Saharan Africa (similar numbers are found in West Asia and North Africa), but clearly the gap between what was promised and what is likely to happen is widening.

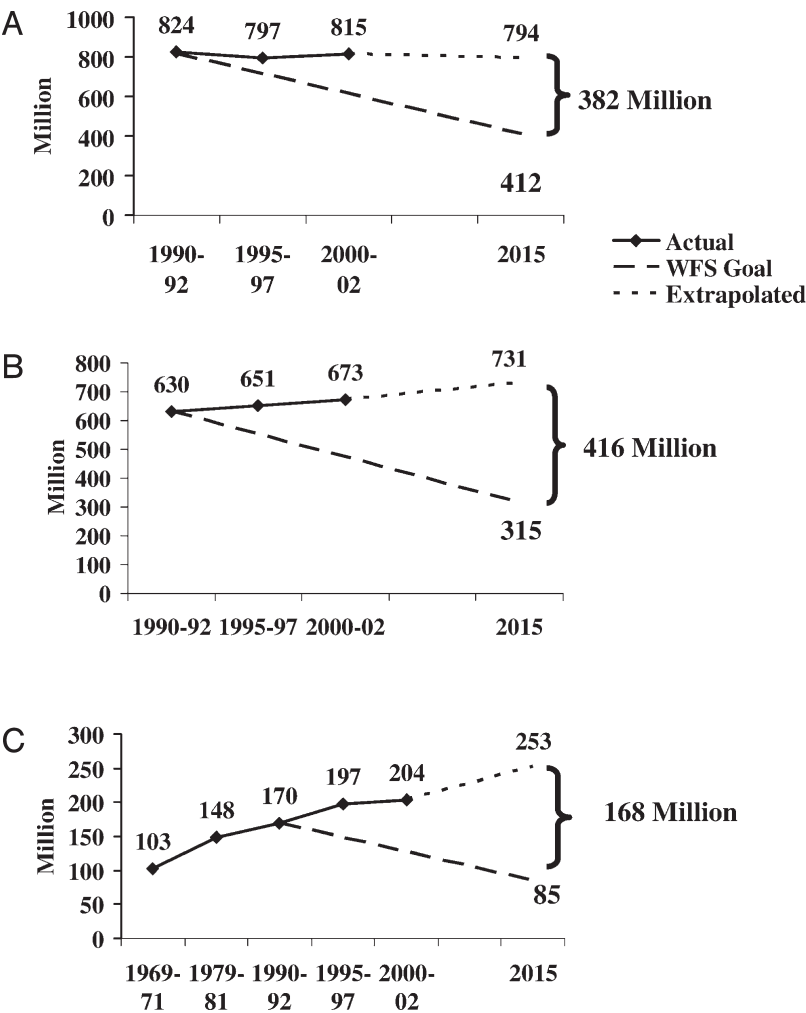


Figure 1.1 Global progress towards meeting the World Food Summit (WFS) goal. (A) Global figures, (B) Global excluding China, (C) Sub-Saharan Africa.

1.4

Hidden Hunger and Obesity

Hidden hunger is generally related to micronutrient deficiency. The data in Figure 1.2 show that among preschool children in South and Southeast Asia, more than 60% suffer from iron-deficiency anemia. This huge public health problem might be resolved simply by a greater consumption of digestible iron. Likewise, in South and Southeast Asia, approximately 76% of pregnant women suffer from iron-deficiency anemia – this again is a major public health problem that is rarely discussed.

The third burden of malnutrition – obesity and overweight – is notably problematic in the United States, where some 63% of the population is either overweight or obese (Figure 1.3A). The US is followed by Mexico and the United Kingdom. At present, at the bottom of the league is Japan which, with approximately 25% of the population being obese or overweight, has managed to maintain this particular epidemic at much lower levels than have most other countries. One major problem is that obesity and overweight are becoming a very serious public health problem in middle-income developing countries, such as China. But this is not only a public health problem, it is also an economic, growth and development problem because it affects the extent to which countries can achieve economic growth. The data shown in

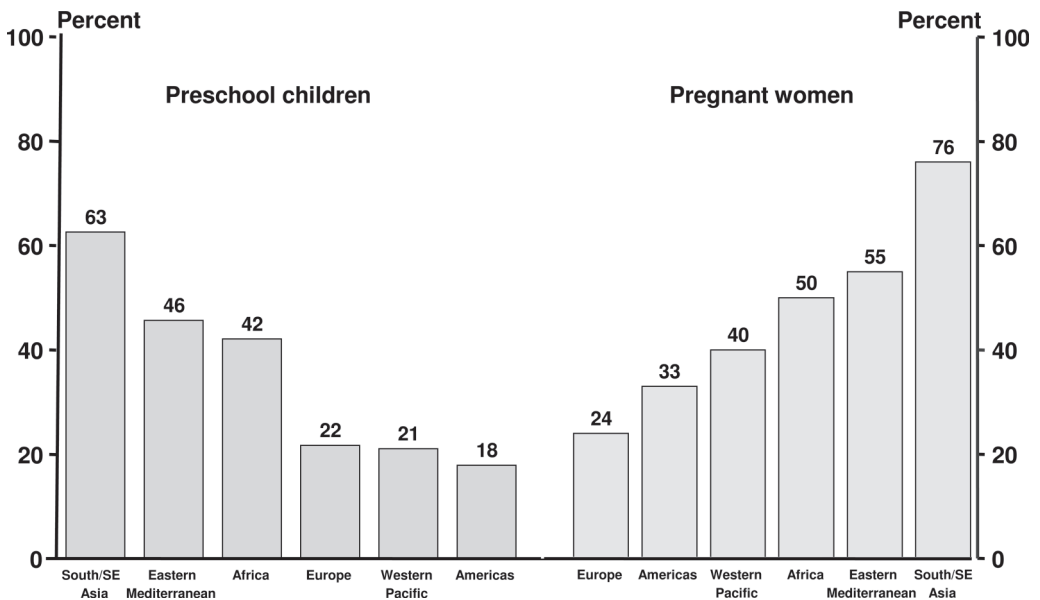


Figure 1.2 Prevalence of anemia in preschool children and pregnant women.
(Source: UN-SCN/ACC, 1999).

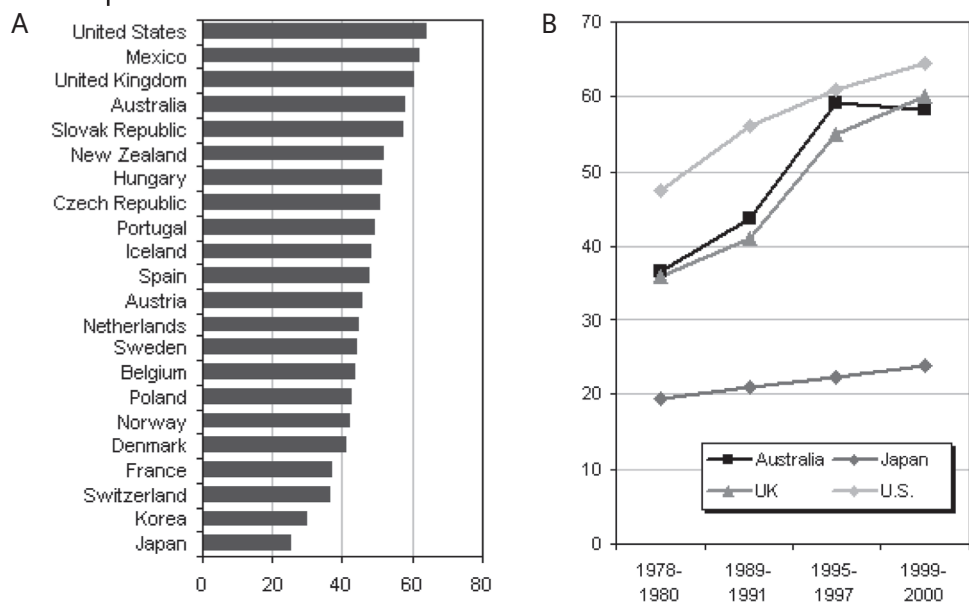


Figure 1.3 Overweight and obese individuals in selected countries.
 (A) Percentage of obese and overweight population by country.
 (B) Percentage of obese and overweight individuals in selected countries, 1978–2000. (Source: OECD Health Statistics, 2004).

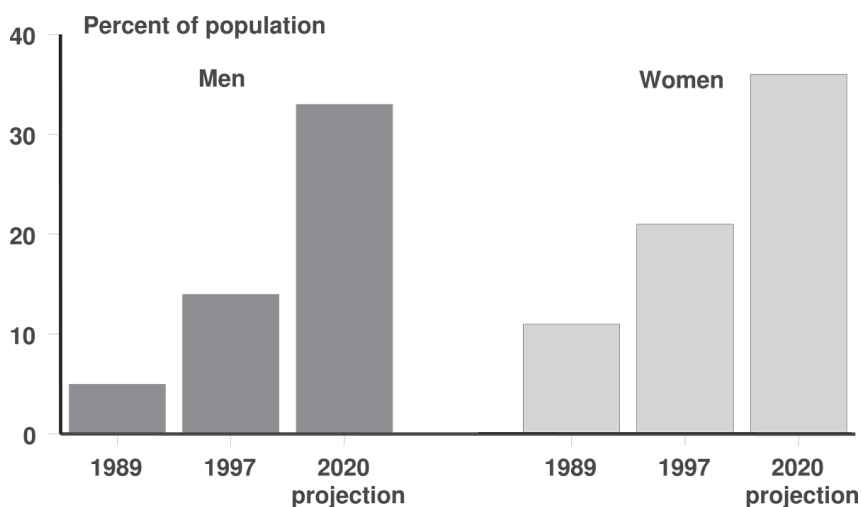


Figure 1.4 Prevalence of overweight in China.
 (Source: Gillespie and Haddad, *Attacking the Double Burden of Malnutrition in Asia*, IFPRI, 2000).

Figure 1.3B indicate that Japan is perhaps performing better than the US, Australia and the UK, where the proportion of obese and overweight individuals is rising very rapidly. The problem is not limited to high-income countries, however – it also occurs in rapidly growing middle-income and, in some cases, low-income countries. The proportion of the Chinese population suffering from overweight and obesity is likely to rise to one-third by the year 2020 (Figure 1.4). The problem here is that obesity leads to chronic diseases, and in doing so places a huge burden on the country's health budget. This in turn has a negative effect on economic growth, and is also associated with extensive human suffering. Although the situation is clearly not as serious as small children dying from a lack of food, it will have very serious consequences. One explanation for these changes is the alterations in diet – referred to as the “diet transition” – although a sedentary lifestyle represents a similarly adverse problem. Today, much less energy is expended than in the past, as many workers spend much time sitting at desks, and we travel in automobiles and airplanes.

1.5

Dietary Change

In today's world, there is an increased food intake, due mainly to dietary changes. Root crops and certain staple fruits are less preferred, and so their consumption relative to that of other foods is falling. Some grains have fallen from the diet, but other foods such as fruits and vegetables have entered. However, animal products, processed fruits, refined sugars, oils and fats are also entering the diet. According to nutritionists, less than 30% of dietary calories should be contributed by fat. In China, for example, the proportion of the urban Chinese population that obtains more than 30% of their energy supplies from fat has increased over a four-year period from 19% to over 33%. It must be remembered that this has occurred among low-income people, and that among high-income people the situation has been far worse, the intake value having risen from about 25% to 67%. There are, therefore, major dietary changes taking place, not only in rapidly growing economies but also in high-income countries.

1.6

Agricultural Research and Policy: Can they Improve Nutrition?

There are several ways in which agricultural research and policy can create improvements in nutrition (Figure 1.5). First, incomes among the poor must be increased. About 70% of the world's poor people live in the rural areas of

How could agricultural research and policy improve nutrition?

- Increase incomes among the poor
 - through productivity increases
 - through better infrastructure, markets, education, health
- Reduce unit-costs
 - through higher incomes and lower prices
- Reduce risks and fluctuations
- Improve diet composition
 - through commodity priorities in research
 - through adequate price policy
- Improve nutrient content of individual foods
 - through industrial fortification
 - through biofortification
- Reduce energy expenditure
 - through increased labor productivity
 - through reduction of heavy labor

Figure 1.5 Opportunities to improve nutrition in poor countries.

developing countries, and depend on agriculture for their upkeep. Thus, there is need to help these people increase productivity in a way that lowers the unit cost. In this way, the consumers can obtain better access to more food at lower prices, whilst the producers can increase their income. It must be remembered that poor consumers may spend up to 70% of their income on food. The Green Revolution reduced the cost of food (or rather the cost of producing a unit of rice and wheat) by 40%. Much of that saving was passed on to consumers in the form of lower prices, and this has had a major impact in terms of the real income of consumers. Another little-discussed aspect was that the largest beneficiary of the Green Revolution was most likely the consumer, because he or she survived and was able to buy more food with the same amount of money. The producers also managed to retain some of the economic gain, and so of course also became better off. But the solution to this problem is not simply to increase productivity, whether via agricultural research or other productivity-increasing measures. It is also very much a matter of investing in a country's infrastructure, making the markets work, and investing in primary healthcare and primary education.

The second point is that agricultural research can reduce unit costs by producing more for the same amount of input or resources. This in turn generates higher incomes among producers, and at the same time lowers the prices for consumers.

Agricultural research and policy can also reduce risks and fluctuations. Much of the malnutrition and hunger seen in developing countries is caused by fluctuations. For example, when the drought hits, there is no food and there is no buffer. Consequently, the children starve, and so also ultimately do the adults. When insects attack crops pre-harvest, or when plant diseases attack the crops, agricultural research can of course play a tremendous role – and has done so on many occasions in the past.

Another approach might be to improve the dietary composition. Figure 1.6 illustrates the percentage change in cereal and pulses production and in population between 1965 and 1999 in selected South Asian countries, India, Pakistan and Bangladesh. The huge increase in cereal production was caused primarily by the Green Revolution and associated changes in production pattern, such as better fertilizer use and better water management. However, pulse production rose very little, mainly because it was more profitable to produce rice and wheat, and that area is where the technological advances took place. Minimal technological changes were made in pulse production, largely because research resources were not invested in those crops. According to agricultural researchers, improving pulse crops is very difficult. That may

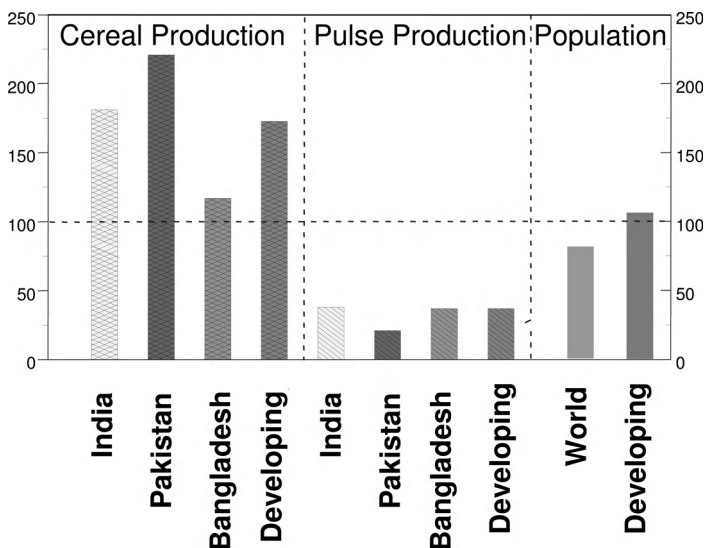


Figure 1.6 Changes (%) in agricultural production and in population between 1965 and 1999. (Source: FAO, 1999).

be the case, but it is certainly not impossible. Maybe with the help of molecular biology the situation will change. In any case, the minimal rise in pulse production and consumption was accompanied by a rapid increase in iron-deficiency anemia in South Asia during the same period of time. Whether there is a causal link between the two events is unclear, but the result illustrates the tremendous influence of setting priorities in agricultural research. The prices for basic staples such as wheat and rice, for which there was rapid technological change taking place, fell sharply, whereas the prices of pulses and livestock – where there was a very limited investment in agricultural research – rose, as shown in Figure 1.7 for Bangladesh. Inevitably, the consumers responded to these changes in relative prices by eating more wheat and rice and less pulses and less animal products, with associated health implications.

Improving the nutrient content of individual foods relates directly to changing the dietary composition (see Figure 1.5) and also providing consumers with an incentive to change the dietary composition. For example, a piece of meat certainly is a good dietary item that everybody ought to have. But if everybody can afford meat, the quantities eaten become ever larger to a point where it is no longer beneficial. The point to be made here is that it is impossible to apply the same policy to solve hunger problems as can be applied to solve problems of overweight and obesity, and the associated health problems.

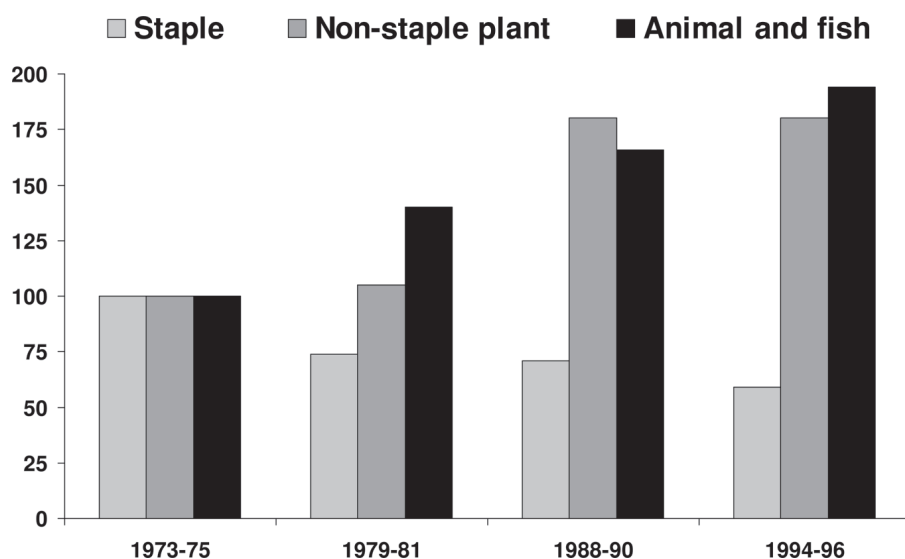


Figure 1.7 Inflation-adjusted price indices for selected foods in Bangladesh.

1.7

Bio-fortification

The next point relates to controlling the nutrient content of a particular food – termed “bio-fortification”. The question should be asked whether it is possible to build into a seed more of the micronutrients that are deficient in the diet, such that the people will consume the product produced by that seed? The answer to this is, yes, an example being the high-quality protein maize produced by CIMMYT, one of the centers supported by the Consultative Group For International Agriculture Research (CGIAR). Currently, the CGIAR is using bio-fortification to build into the seeds of staple food commodities greater amounts of iron, zinc, and vitamin A, and in a form that is digestible. In “Golden Rice” (see Chapter 5), which to date has achieved success only at the research level, an increased iron content was built into the rice, using transgenic methods.

At present, most bio-fortifications performed at the CGIAR are based on more traditional plant breeding, using molecular markers. This does not imply a fear of genetic engineering; rather, it has not yet emerged as the key method, although it may well be in the future. Bio-fortification offers tremendous opportunities, for example, if missing nutrients can be built into those foods that poor people can afford to buy, at least until such time as they escape poverty and can purchase some meat or perhaps a little more fresh legume so that they have a more diverse diet. The ultimate solution in this situation is to create a diverse diet, but that means to abolish poverty. In the meantime, bio-fortification has a very important role to play. Industrial fortification has been used for many years, and also has an important role to play, primarily for those consumers who buy processed food and who, living in the larger population centers, can be easily reached by industrially fortified foods.

Agricultural research and policy can also reduce energy expenditure, but this is potentially problematic for people in developed countries – who in fact need to expend more energy to avoid obesity. The aim would be to reduce the energy expenditure of the hungry; increasing labor productivity so that people will not need to work so hard to earn the same amount of money. By reducing heavy labor such as weeding or digging ditches, and by increasing labor productivity it should be possible to reduce energy expenditure among those population groups that suffer hunger.

1.8

Agricultural Research and Nutrition Goals

The question of whether nutrition goals should guide agriculture research and policy depends on the relative importance of the nutrition goal, relative to the other goals pursued. One factor here is cost effectiveness, and whether there are easier, better or less expensive ways of achieving a nutrition goal, and whether such alternative routes might be pursued. It is probable, however, that trade-offs will have to be made with other goals, as it is unlikely that the same research strategy and the same set of policies will alleviate both hunger and obesity. This situation also depends on whether the nutrition goal is compatible with economic demand, because if it is not then those farmers who heeded the word of the nutritionists will suffer financial ruin because they cannot sell the product at a reasonable price. When the farmers have produced the food, only the consumer demand determines what the market price will be.

Finally, it is perhaps pertinent to mention the influence of governments on the market price for food. In developing countries – unlike Europe – the governments are much less likely to provide subsidies.

1.9

Factors Influencing Food Demand

Food production must be compatible with economic demeanor. A variety of factors are influential when people decide what food to buy, and these include population growth, income changes, price changes and organization (Figure 1.8). Nutritional value is also applicable here, although usually consumers do


- 
- Population growth
 - Income change
 - Price change
 - Urbanization
 - Food safety
 - Organic foods
 - Locally produced foods
 - Identity preservation

Figure 1.8 Factors influencing food demand.

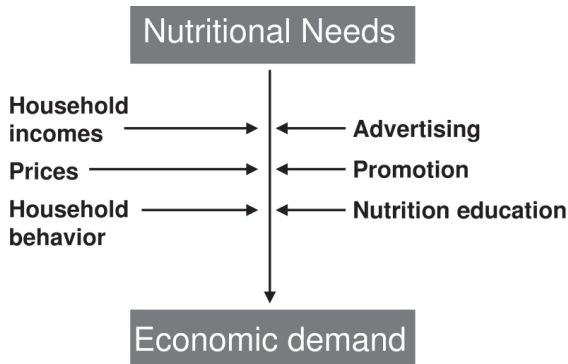


Figure 1.9 Factors shaping economic demand.

not demand food on the basis of its nutrient content. This is a very important issue, because if nutritional need becomes the dominant factor and what actually sells in the market is forgotten, then any help provided to the farmers is nullified.

But people are becoming much more aware – particularly in high-income countries – partly because educational levels are rising, but mostly because they can afford to spend more money on nutritionally better food. More and more people do read food labels (especially in the US, where the labeling is better) before buying food.

There are six factors that help to determine whether nutrition needs are equal to economic demand (Figure 1.9). As incomes rise, then economic demand may become closer to nutrition needs at the lower end – the hunger end. And the opposite may be true at the higher end – the obesity end. Prices also influence household behavior, whilst advertising, promotion and nutrition education are very important when persuading consumers to focus their buying of food on what is nutritionally best for them. Without nutrition education, and without advertising – or with the wrong type of advertising – the gap between nutritional needs and economic demand may in fact widen.

1.10 Summary

In conclusion, malnutrition is causing widespread human suffering, major economic losses, and premature deaths. Agricultural research and policy can play a major role in the alleviation of this situation, whether via under- or over-nutrition. The coexistence of under- and over-nutrition calls for targeted priorities; poor people who cannot afford to buy meat, but would like to do so, should be provided with meat. But those people in wealthy countries should

not double their meat consumption, as from a healthcare standpoint this is not good. It is essential therefore that these priorities are targeted. Priority settings should consider both energy/protein deficiencies and micronutrient deficiencies, and both factors must be examined closely because they are equally important. When everybody worldwide has escaped poverty it may be possible to relax, but this will not occur for many decades. Until then, the compatibility of nutrition goals and consumer demand remains all-important.

Author Biography

Philip Bloomer



Head of Advocacy & Head of Oxfam International's Make Trade Fair Campaign, Oxfam

Phil Bloomer is the Head of Oxfam International's campaign to Make Trade Fair. The Global Campaign is focused on achieving trade rules that work for the poor as well as the rich. In the last four years he has led Oxfam's campaigning work on agriculture, coffee, patents and medicines. Phil is also the Head of Advocacy at Oxfam running teams responsible for research policy development and lobby. Phil previously worked for 11 years in Latin America on international economic justice issues and human rights.

2

How Can Agriculture and Trade Contribute to Sustainable Livelihoods for All?

Philip Bloomer

2.1

Introduction

The life sciences have an enormous potential to contribute when addressing some of the Earth's greatest challenges, but too often that potential is either blocked or overwhelmed by the current course of globalization. Oxfam's proposal is that, by working together, that course of globalization can be shifted and, in turn, the potential of science and technology can be released to help to create public goods that directly benefit the poorest inhabitants of the planet. In Chapter 1, Dr. Pinstrup-Andersen referred to those public goods that must be created rapidly during the next decade. Today's world is one of unprecedented wealth, alongside obscene inequality, with one billion of the Earth's citizens living on an income of less than US\$ 1 per day, and half of the population living on just US\$ 2 per day. Some 80% of the world's total wealth is owned by only 20% of its population. Today, the current model of globalization – including technological revolution – is proving to be a highly successful generator of wealth. Tragically, however, it is failing to distribute that wealth around the planet – and it is failing many of the poorest people. For many poor people, experience of that globalization is unfortunately seen as a source of increasing insecurity, increasing vulnerability, and – at least in Sub-Saharan Africa – increasing poverty. Consequently, the present model of globalization is also a source of international insecurity. This is not a failure of science and technology, but is rather a failure of global and economic systems. Thus, the greatest challenge faced today is to create a model of globalization that promotes just and fair outcomes for all. The current generation of humans on this planet is the first to have had the potential to eliminate absolute poverty. That is a vast task, and is undeniably the greatest challenge that the current generation will face. More importantly, to have that potential and yet not realize it will be condemned by future generations.

2.2

The Global Trade Rules

In today's world, technology and science have a critical role to play, but they must be harnessed as they were in the Green Revolution for that end. Sustainable agriculture is the fundamental challenge, and with 70% of the world's population living in rural areas, there is no genetic or environmental reason why 800 million people should go to bed hungry tonight. Amartya Sen, the Nobel economics laureate, said that, "... there has never been a famine in a country with a functioning democracy". In other words, such suffering occurs because of the powerless position of those who will go to bed hungry.

There are many driving forces behind this unnecessary suffering. One of the fundamental reasons why such suffering continues is that global trade rules reflect that powerlessness, and are rigged against the poor, and this is particularly true in the case of agricultural trade. If some of the poverty problems about which Dr. Pinstup-Andersen spoke are to be addressed, it is vital that mankind is serious about them. This is the very reason why Oxfam and many other organizations around the world are focusing their energy on the current negotiations of the World Trade Organization (WTO). There is a real opportunity in those negotiations to achieve a substantial shift in global trade rules, to make them work for the poor as well as for the rich. The enhancement of the prospects for poverty reduction that this would create would also be a significant shift in the course of globalization. At present, however, the prospects for those negotiations appear poor, with most European Union member states and the United States seeming to be determined to hold on to every privilege, every exception and the rigged rules as they attempt to prise open poor country markets for their own agricultural exports.

The danger for big business – and indeed the danger to all – is that this approach is placing enormous strain on the multilateral rules established by the WTO. This is particularly relevant because from now on, developing countries will not be willing to accept the rigged rules and double standards that have characterized global trade in the past. The trade rules in agriculture have benefited a tiny elite of very large farm businesses which currently receive the lion's share of European and American subsidies.

2.2.1

The Case of Cotton

In the US, each year a mere 25 000 cotton farmers receive US\$ 4 billion in subsidies, whilst half of all US farmers – most of whom operate small farms – receive no government support whatsoever. Typically, every US\$ 3 worth of cotton which is exported costs US\$ 4 to produce – which is an economic absurdity. If the democratically elected US government decides to put tax

payers' money into the pockets of very wealthy landowners, it is a possible – albeit highly regressive – step that they can take. But what is not acceptable about this is that the same policy destroys the livelihoods of 10 million cotton farmers and their families in West Africa. In the United States, the subsidies of US\$ 4 billion stimulates a massive overproduction of cotton, and this is dumped on world markets at below cost price. This in turn reduces world prices by 25% and drives many small producers out of business, or at least further into poverty. In 2004, this situation was challenged when the Brazilians, supported by the West Africans, took the case to the WTO, which in turn ruled that every subsidy that the US has in cotton is illegal. On appeal by the US, the ruling of the WTO court was, again, that these subsidies were illegal. The unfortunate sequel to this, however, is that the US now appears determined to hold on to as much as of those subsidies as they possibly can, for as long as they can, probably until 2013, despite their being illegal. On this basis, it can be calculated that, by 2013, there will not be a single West African cotton farmer left to celebrate the end of that pernicious dumping.

2.2.2

The Case of Sugar

Today, Europe spends € 3.30 in subsidies to export US\$ 1 worth of sugar, and consequently the annual cost to the European tax payer of dumping the excess 5 million tons of surplus sugar onto the world markets is € 2 billion. There are winners and losers with this policy, however. Those who benefit are the sugar barons of the UK, France and Germany; these comprise about 100 of the largest farm businesses in Europe who each receive on average around € 300 000 per year in subsidies. The other winners are the top six sugar processors in Europe, who together receive approximately € 1 billion each year in export subsidies. Whilst this is a policy choice of the European Union of elected governments, it cannot be acceptable when it destroys the livelihoods of poor farmers in some of the poorest countries, because these people are the principal losers of such policies. Some of the poorest countries on Earth figure very prominently amongst those losers: Malawi, Mozambique and Ethiopia together lost US\$ 240 million in 2001 alone, while Brazil, South Africa and India each lost around US\$ 60 million in 2002. These figures are losses to the countries, but at ground level they represent lost economic opportunities for small farms and agricultural businesses worldwide that are simply extinguished. This absurd regime has been challenged again at the WTO's court, and the initial ruling is once more that many of the subsidies are outlawed. The European Union again has appealed, but it has been forced to reform its sugar regime this year. This can be done either in a way which benefits poor people, or in a way which does not benefit the poorest who have been so badly affected by the regime to date.

In the least-developed countries, as well as in African, Caribbean and Pacific regions, Oxfam has suggested proposals that would end sugar dumping and which would in turn improve market access for the least-developed countries. This would also ensure that the interests of the African, Caribbean and Pacific countries were properly addressed. However, this will not occur unless there is public outcry across Europe, since the vested interest which receives such large amounts of corporate welfare also has an enormous interest in maintaining the status quo. And of course, they are lobbying hard to retain their benefits.

2.2.3

The Case of Rice

For 3 billion people – half of the world’s population – rice is the staple food. Indeed, in many languages around the world the word “rice” is synonymous with the word “food”. The production of rice also represents an income for over 2 billion people worldwide, many of whom are smallholders in poor countries and grow rice as a means of living.

Although the US is one of the world’s largest exporters of rice, this is a somewhat ironic situation given that the cost of growing rice in the US is about 2.5-fold that in Vietnam or Thailand. So, the only way that the US can sustain its position as one of the major exporters worldwide is to pay massive subsidies to US rice growers. The US is not prevented from paying such subsidies, but this will lead to the destruction of economic opportunities for some of the poorest people on Earth. The wealthy countries now face a major problem in not only trying to sustain the dumping that they have been carrying out consistently for years, but also now trying to prise open some of the poorest country’s markets in order to ensure that there are enhanced opportunities to export their products. An example of where such pressure had a heavy impact was Haiti, where in 1995 the International Monetary Fund enforced a massive cut in tariffs on rice, from 35% to just 3%. The US exports of dumped rice to Haiti skyrocketed immediately, such that today three-fourths of the rice eaten in Haiti is from the US. This was good news for companies such as Riceland Foods in Arkansas, which is one of the biggest rice millers in the world, as their profits have soared. However, it had devastating impacts on the low-cost rice producers in Haiti, and today those rice-growing areas have some of the highest levels of poverty and malnutrition in Haiti, which is already one of the poorest countries in the world. A similar situation occurred in Honduras.

The real danger is that this policy – which has led to so much unnecessary suffering – is now being imposed across poor countries at the WTO. The danger here is that the developing countries would essentially be unable to apply tariffs to protect vulnerable farm sectors from low-cost imports, and particularly from dumped exports from the US and Europe. Poor countries

must have that power in order to enhance their own food security and their rural livelihoods. The question must be asked as to how the 550 million poor people in rural India would fare if the country were to be pressured by the WTO to open up its food markets to dumped food from the US and Europe? Clearly, a global coalition is needed to persuade the US and the European Union to stop forcing these disastrous policies on the world, the point being that in the face of this injustice, the benefits of any major scientific innovation will at best be swimming against the tide.

2.3

Investments in Scientific and Technological Innovation in Agriculture

Although agricultural research may impact heavily on specific problems in poverty, the economic and political systems involved have, as yet, failed to follow the same route. Indeed, in many ways the movement is against the tide and any benefits that scientific innovation has created in the past are now being pushed back. In agriculture, as in medicine, there is very great difficulty in ensuring the correct level of investment for poor people. Essentially, it is clear that the market alone will not stimulate the new technologies necessary to support poor farmers, because the potential return or profits have so far been simply insufficient to stimulate investment in new technological solutions for poor farmers. Therefore, it is essential that major new public investment is acquired for research and development alongside private investment (where it exists). This scientific and technological research agenda must be developed in cooperation with poor farmers, and address problems based on their priorities. To date, however, this has not generally happened, even in the case of genetically engineered crops. For example, very little investment has been made in the five most important crops for semi-arid tropics: sorghum, millet, pigeon pea, chickpea, and groundnut. It is unlikely that these transgenic crops will be the most effective investments to deal with food and security in poor countries in many cases over the next era. Patents which are fundamental to the development of transgenic crops may be either a hope or a hindrance in creating those innovations necessary to sustainable agriculture, but future development will depend entirely on the form that these patents take.

Patents are a “social contract”, where society grants higher prices on products in return for innovation, although the current global rules of the WTO for patents represent a very bad social contract for poor countries. According to the World Bank alone, the intellectual property rules that are now within the TRIPS agreement of the WTO will provoke an outflow of US\$ 20 billion from developing countries to rich countries each year, although this will not have any major impact on poor people’s access to lifesaving medicines such as

antiretrovirals. Oxfam is not against patents, and believes that there can be a social contract where higher prices can be paid for that innovation; however, the world needs intellectual property rules that will work for the poor as well as the rich. As yet, the social contract held globally does not represent that kind of system. Recently, the Nobel Laureate John Sulston spoke out clearly against a simple universal application of very lengthy patents as enshrined in the WTO, and noted that these may be harmful and mitigate against the technological innovation that is necessary for poor farmers.

2.4

Summary

To conclude, the present generation is the first to have an opportunity to eliminate the scourge of poverty on Earth. Science and technology have vital roles to play, but they will only realize their full potential if there is a model of globalization that functions for the poor, as well as for the rich, and ensures distribution of the benefits of scientific innovation. A major opportunity to shift the current faulty model will occur at the WTO talks over the next two years, but in order to confront and defeat the vested interest that is holding out for the status quo and is desperate to hold onto that privilege, a massive global coalition is needed that includes scientists and companies working alongside civil society and politicians. It will be in everybody's interest if a sustainable and secure planet can be ensured for future generations. Moreover, a concerted campaign is needed to shift the course of globalization onto a sustainable path where life sciences can play a critical role in overcoming poverty and contributing to human security and sustainable development. By working together, this can be achieved.

Author Biography

Bernward Garthoff



Member of the Board of Management, Bayer CropScience

Since July 1, 2002, Dr. Bernward Garthoff has been a member of the Board of Management and responsible for Research and Development at the Bayer CropScience AG.

He was born on November 2, 1948 in Ratingen, Germany. He studied veterinary medicine at Hannover University. Following the award of his doctorate in 1975 and a period of scientific work, he joined Bayer in 1976 and exercised a variety of functions in pharmacological research.

In 1987 Bernward Garthoff took on responsibility for the extension of the Miles Research Center in West Haven, Connecticut. One year later he returned to Germany to head the Institute for Pharmacology in Wuppertal, before transferring back to the United States in 1989 as Senior Vice President for Research and Development at Bayer's then U.S. pharmaceuticals subsidiary, Miles.

He returned to Germany again in 1992 to become Head of the Institute for Cardiovascular and Arteriosclerosis Research. He moved to the Crop Protection Business Group in 1994, becoming Head of Portfolio Management in April of that year. He has recently managed the integration process entrained by the acquisition of Aventis CropScience.

3

Plant Biotechnology: A Contribution to Sustainable Agriculture

Bernward Garthoff

3.1

Introduction

The following perspective is based on my experience as the head of R&D of our company, Bayer CropScience, which, although relatively young, has ancestry from Rhone-Poulenc, Bayer, Hoechst and Schering totaling some 548 years.

Plant biotechnology must be considered in terms of future developments, and within the setting of a sustainable agriculture concept which has been in the pipeline since 1987, just five years after the introduction of transgenic crops in June 1982. This major advance was developed at the Cologne Max-Planck Institute by Professor Jozef Schell who, at the time, maintained that the procedure would revolutionize agriculture. In response, the media reporters at the time showed utter disbelief!

It is first necessary to examine the “three pillars” of sustainable agriculture: economic viability, environmental responsibility and social acceptability. With regard to the subject of agricultural research, as referred to by Dr. Pinstруп-Andersen in Chapter 1, it is worth repeating a quotation from the United Nation’s Food and Agriculture Organization (FAO): “Agriculture in the 21st century is facing unprecedented challenges. An additional two billion people will have to be fed over the next 30 years from an increasingly fragile national resource base. More than 70% of the world’s poor still live in rural areas and depend on agriculture for their survival. Agricultural research – including biotechnology – holds an important key to meeting their needs”.

3.2

The Impact of Plant Biotechnology

From an agricultural standpoint, the total cultivated area worldwide is limited at 1.5 billion hectares, and it is known that in the future the used area will decrease from 0.5 to 0.17 hectare per inhabitant. It is often forgotten that in the past productivity was improved by 45%, mainly as a result of using crop protection, but today we are approaching something of a limit here. It appears that biotechnology is a major issue, and its rapid adoption bears testimony to the economic value not only in industrialized countries but also in developing countries. The major increase in global area utilized for biotech crops, and specifically the increase of at least 20% during 2004, has occurred in areas such as China and India (Figure 3.1). Perhaps surprisingly, this increase is largely due to the efforts of the smaller farming businesses of these countries.

We are currently faced with a 10 : 1 ratio of private versus public funding in plant R&D. There is also a 4 : 1 ratio in public sector funding in industrialized versus developing countries, with a private sector spending of approximately US\$ 1 billion in industrialized countries (Table 3.1). By comparison, only US\$ 250 million is spent in developing countries, with much of that being derived from their own resources and public foreign aid, though some funds are provided by the Consultative Group for International Agriculture Research (CGIAR). Full details of the private sector are not really known.

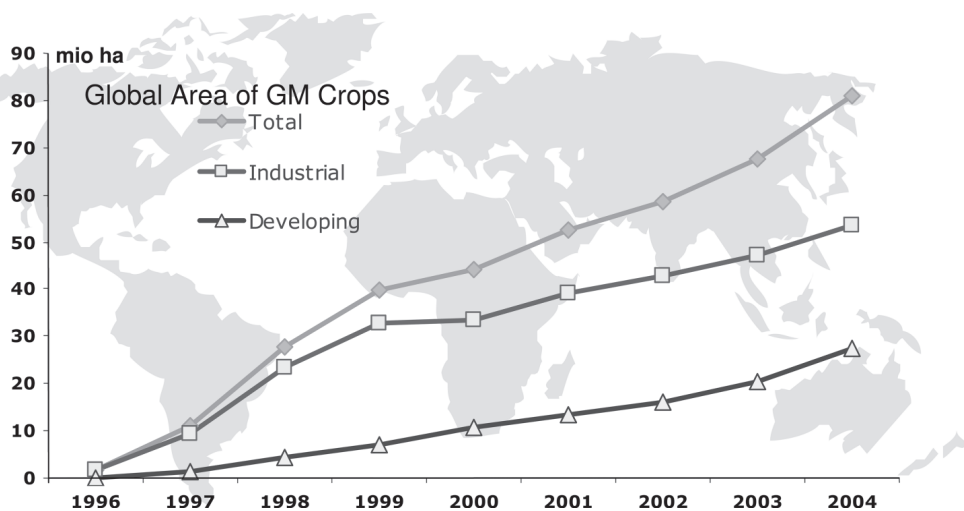


Figure 3.1 Global increase in biotech crops.

(Source: International Service for the Acquisition of Agri-biotech Applications (ISAA) report, 2004).

Table 3.1 Global spending on biotechnology research.
(Source: Byerlee and Fischer, 2001).

Country and sector	Annual biotechnology R&D budget [US\$ million]
<i>Industrial countries</i>	1900–2500
Private sector	1000–1500
Public sector	900–1000
<i>Developing countries</i>	165–250
Public (own resources)	100–150
Public (foreign aid)	40–50
CGIAR centers	25–50
Private sector	Unknown
<i>World total</i>	2065–2750

CGIAR: Consultative Group for International Agriculture Research.

In a recent study conducted by the International Food Policy Research Institute (IFPRI) (see Cohen, J., *Nature Biotechnology* 23, 27–33, 2005), it was revealed that the plant biotech research pipeline in developing countries contained 201 events for 45 different crops. This study also declared that “... GM crops developed by public research institutes should be most relevant to local needs in poor countries”, and “... unfortunately, most poor countries lack the knowledge, capacity and funding to develop and comply with bio-safety regulatory requirements, as a result, gene-modified crops face difficulties moving from the lab to farmers’ fields”. In my view this is the decisive sentence.

There appears to be a distinct lack of downstream development capacity, despite local crops being developed in research. On the other hand, the biotech industry excels at downstream development, and this is vital if goals are to be achieved. Bearing this in mind, within the private sector committee of CGIAR, a proposal was voiced at the annual meeting in Mexico to conduct a special program, referred to as the Scientific and Knowledge Exchange Program (SKEP). The proposal made to the CGIAR was to create an exchange between the private sector and the different directors of the different institutions of CGIAR. This type of private/public partnership should be followed up, since it will promote activity in this field.

3.2.1

Economic Benefits Today

An agreement being reached from both sides to exchange knowledge clearly represents the way forward from an industry point of view. The adoption of biotechnology has already indicated that this approach will provide economic benefits and lead to higher farming returns, as indicated by fewer crop inputs and lower production costs. An example of this is a herbicide-tolerant crop, with associated reductions in herbicide costs, as well as insect-resistant crops. A typical insect-resistant crop of *Bacillus thuringiensis* (Bt) cotton is illustrated in Figure 3.2, grown side by side with a standard cotton crop. The benefits of these new crops are increased yields per hectare, herbicide tolerance and insect resistance with the effective control of targeted insect pests. In fact, this achievement is supplementary to what can be achieved using classical crop protection systems. Moreover, seed treatment can still be carried out using both classical and GM technologies.

Overall, simplified crop management and reduced production costs accounted for an estimated increase in crop value of US\$ 1.5 billion in 2003, which included a 20% share in developing countries (US\$ 300 million). The use of insect-resistant crops led to an increase in estimated crop value of US\$ 1 billion in 2003, and over 90% of that was achieved by resource-poor farmers in developing countries.



Figure 3.2 Cotton field planted with normal cotton (left) and insect-resistant Bt cotton (right).

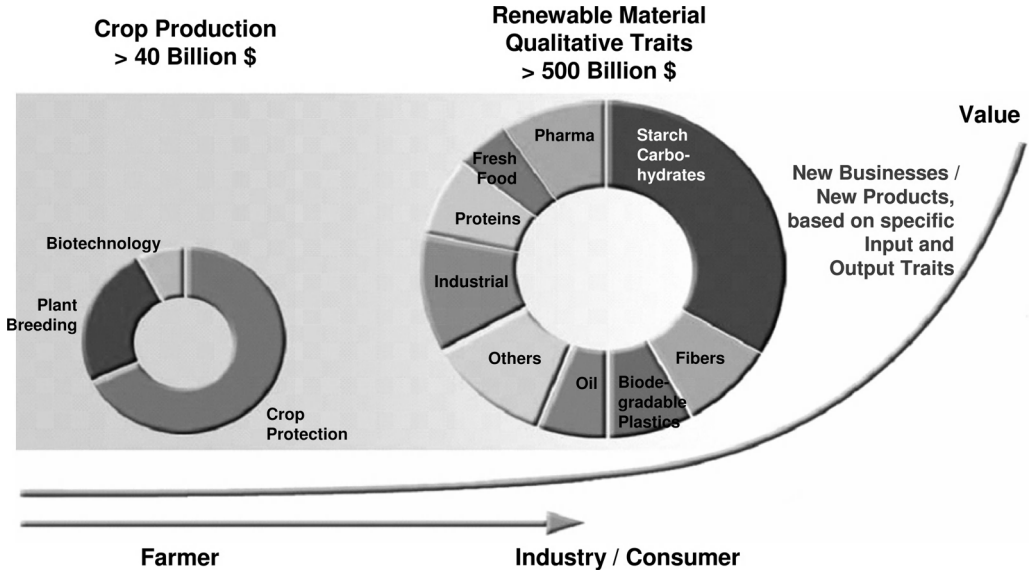


Figure 3.3 Heading for a bio-based economy.

3.2.2

The Economic Benefits of Tomorrow

What, then, will be the economic benefits of tomorrow? It is clear that agriculture is heading for a bio-based economy (Figure 3.3), and future plant breeding will be targeted specifically at those minor crops referred to by the CGIAR. It is clear that selective plant breeding is required, and that the biotechnology of the future will have a major impact in this area. Part of the crop protection and biotechnology approach will result in the evolution of new products, including biodegradable plastics, proteins, pharmaceuticals, and proteins derived from plant-made pharmaceuticals. With biotechnology, the movement is towards the consumer and the industry.

3.3

Environmental Responsibility

As a company, it is essential that Bayer CropScience takes care to maintain general environmental benefits through plant biotechnology, such that balanced resource management can be achieved. And whichever version is taken in terms of sustainability, it must be balanced in those terms. With this in mind, crop protection products will be used where they are needed, as will biotechnology. In fact, most of the resources described here relate not only to

the area of soil and food but also to that of water. So, there must be a perspective – a goal for the future for these new products, and for other new activities and technologies and products. The future clearly lies in areas such as resource and fuel management.

Agronomic traits reduce agriculture's footprint. An example of this is herbicide tolerance, which is helping to conserve soil in some countries. There will also be a reduction in fuel consumption by farm machinery, and consequent reductions in associated emissions. Indeed, a recent Canadian study conducted by the Canola Council showed there to be a fuel reduction of 31.2 million liters, due simply to the use of herbicide-tolerant GM canola. And there is an additional benefit, because the use of biotechnology leads in turn to the protection of biodiversity by preserving available land and avoiding further deforestation.

Among resources worldwide, water is perhaps one of the most scarce, with 70% of all water being used for agriculture. The International Water Management Institute even maintains that approximately 90% of all water resources are used for food production. However, whilst the production of enough meat to feed one person requires 5000 L per day, a vegetarian diet requires only 1000–2000 L each day. Put another way, it requires 1800 L to produce 1 kg of wheat, but 9700 kg to produce 1 kg of beef. Clearly, water is the single commodity that must be conserved in the future. The UN commission for sustainable development has recently stated that “Biotechnology research has yielded positive results in terms of enhanced crop yields per liter of water consumed”. The future use of drought-tolerant crops holds promise for even greater efficiency in that respect.

Biotechnology is also preserving the remaining natural areas in which to conduct research into plants with built-in tolerances against adverse conditions such as stress, heat, cold, drought, field salinity and acidity. By taking this approach, it is possible that even marginal land can, in the future, be utilized as farmland.

3.4

Societal Benefits

Societal benefits today represent the third pillar in the area of sustainable agriculture. Increased yields and productivity contribute to a greater global food sufficiency, and benefits become clear in both industrialized and in developing countries. These include reduced production costs of agricultural produce, high-quality food and fiber, and increased investment and innovation, diversification and the growth of rural economies. It will also provide more affordable and consistently available levels of food and feed supply, and help to alleviate poverty among smaller farm businesses (Figure 3.4).

<u>Economy</u>	<u>Environment</u>	<u>Society</u>
<ul style="list-style-type: none"> ▪ Enhancing Efficiency ▪ Improving Competitiveness 	<ul style="list-style-type: none"> ▪ Reducing Environmental Impact ▪ Saving Resources 	<ul style="list-style-type: none"> ▪ Safeguarding Food Supply ▪ Promoting Nutritional & Health Benefits
		

Figure 3.4 The contribution of plant biotechnology to sustainable agriculture.

In the future, there will be further direct advantages to consumers, paving the way to embrace the full benefits of plant biotechnology and to create novel products that will promote and protect both human and animal health. Subsequently, high-quality foods and fibers will show major improvements over those commodities available today. Most importantly, with the introduction of plant biotechnology-produced regional crops and varieties there will be a stabilized food supply to provide for growing populations.

3.5 Summary

It is clear that, from Bayer CropScience's point of view, plant biotechnology is able to make major contributions to sustainable agriculture. From an economic standpoint, this means enhanced efficiency, improved competitiveness and, from an environmental perspective, reductions in environmental impact and the preservation of resources. From society's point of view, it means the safeguarding of food supplies and the promotion of nutrition and health benefits. Of course there will be stumbling blocks along the way, with one of the issues being a non-unified regulatory area, and the question of regulatory areas in developing world. To overcome this problem, we have to have a joint effort. In that regard, I think plant biotechnology offers a starting point for a closer collaboration between the developed and the developing world.

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Module II

Access to Food for All

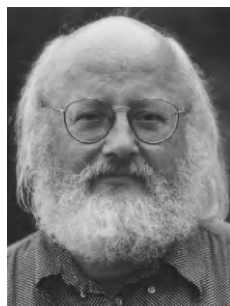
Introduction

Dominique Lecourt

The world map speaks for itself: 75% of the billion and half human beings earning less than 1 euro per day earn their livelihood through agricultural activity, living on small-scale farms on disinherited land. Hunger touches more than 800 million people including 300 million children, and two billion suffer from malnutrition! These and other facts enable us to measure the breadth of this human scandal, which constitutes the great tragedy of our time in spite of the progress made by China and India. The evolution of our planet does not invite optimism: the amount of cultivated land has not increased in 50 years; on the contrary, it has decreased. At the same time deforestation continues to increase. It appears from now on difficult to achieve the goal laid down in 1996 by the World Food Summit which invited us to reduce by half the number of people suffering from chronic malnutrition by the year 2015. What measures could be implemented to improve this situation? How can the world agricultural markets be adjusted so that the poorest can be nourished? Fear, which is the dominant feeling in our society, might inspire too strict regulations that could deprive the poorest people of the resources without which they are unable to survive. The case of golden rice can be used to illustrate this. To avoid such dramas, how can we encourage public discussion in order to better evaluate the risks? Won't we succeed in this regard by using standards in agriculture which favour poverty reduction, while also respecting the environment and economically necessities?

Author Biography

Klaus Ammann



Director, University of Bern Botanical Garden

Klaus Ammann (born 1940) obtained a PhD thesis on vegetation history in 1972. Since 1996 he is the director of the Botanical Garden at the University of Bern. Since 2000, he is also Professor h.c. at the University of Bern.

He regularly teaches lectures in Plant Systematics and Evolution, Biogeography; Air Pollution Biomonitoring at the Federal Institute of Technology in Zurich. He is a member of many national and international committees, among others the European Group of Plant Specialists, IUCN, and the Biosafety Committee of the Government of Switzerland.

His current research is focused on the chemotaxonomy of macro-lichens, calibrated biomonitoring of air pollution with lichens, molecular systematics with lichens, ecological monitoring, ethnobotany in Jamaica, ecological monitoring in Bulgaria.

He is involved in the ecological risk assessment of vertical gene flow in Switzerland under the EU Projects AIGM and SIGMEA, as well as two further EU projects on Gene Flow and Plant Conservation of Europe.

He is also a member of the Teaching Faculty on Biosafety at UNIDO, among many more committees.

4

Four Theses on Agriculture, Nutrition and Sustainable Development

Klaus Ammann

This chapter comprises four theses which relate to communication, dialogue and active listening with regard to agriculture, nutrition and sustainable development.

4.1

Thesis 1: Risk

Today, society in Europe is focused on risk, rather than on opportunity. This can be illustrated diagrammatically, with virtual risk – the hypothetical risk – being completely overpowering (Figure 4.1). However, this is somewhat of a paradox when considering the real risks in life, which include smoking and obesity, such that the picture becomes somewhat distorted.

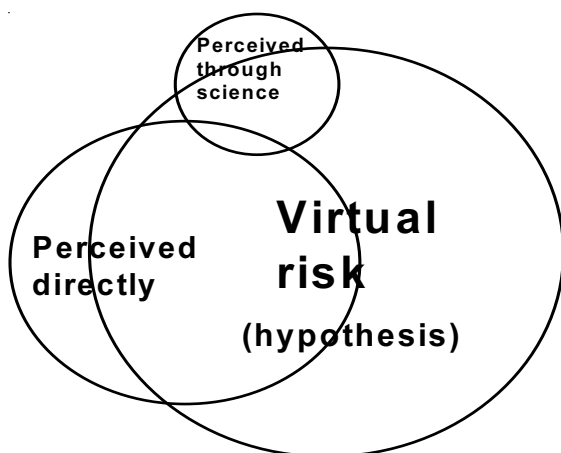


Figure 4.1 We live in a risk minded society. (Modified after J. Adams, 1994).



Figure 4.2 Distorted risk perception.

The “greens” are overly concerned with genetically modified organisms (GMOs), but clearly do not care about cannabis use, which has been proven scientifically to be highly detrimental to both physical and social life (Figure 4.2).

There should not only be complaints – rather, something should actually be done about risk communication. It may be necessary to re-think the term “risk” and to perceive this as the Chinese have always done. In Chinese, the icon of risk itself is a composite of hazards divided through chance, and this has an ancient history (Figure 4.3). When I asked people in China where this terminology came from and how the word risk was defined in the Chinese language, the reply was that it had its roots in military language, whereby generals would regard the hazard of certain attack, but also recognize its benefits. I believe that it would be wise to adapt to this kind of philosophy today.

危机 = 危 + 机

Risk = Hazard / Chance

Figure 4.3 The Chinese wording for risk.

4.2

Thesis 2: Following Up

The “precautionary principle” should not really be referred to here, as it is – strictly speaking – illegal. The Secretary General of the Convention of Biological Diversity was in agreement with this, as were those who ran the bio-safety protocol, where it is termed the “precautionary approach”. Bad English is known to be the Esperanto of science, but it is not difficult to identify the difference between a principle and an approach. This is indeed crucial, and a return should perhaps be made to the clear definitions – how it is in the law, when written down – rather than simply talking about principles. The precautionary approach, as defined in Rio de Janeiro in 1992, is based on scientific facts, on negative trends in the environment, and on proven facts, such as air pollution. The term was introduced because the trends were clearly visible and could be proven scientifically – there was no scientific uncertainty about the negative effects.

The situation is totally different in bio-safety protocols, where it seems to be acceptable to introduce a fundamental change. There, all of a sudden a precautionary principle is established, and this term is abused in Europe by certain governments. Thus, it might be preferable to revive the Organisation for Economic Co-operation and Development (OECD) familiarity approach. For example, a plethora of risk assessment papers has been prepared on certain traits of *Bacillus thuringiensis* (Bt) maize, and millions of dollars have been spent on this type of research. There is, therefore, no need to force the Thai government to repeat such investigations at a cost of another US\$ 3 million. The term “familiarity” should be introduced, accepting that the trait has been treated, the outcome is known, and there may be certain local adaptation problems. But overall the task is complete, and large amounts of money could be saved.

Gandolfini and colleagues published details of their extensive research on 300 non-target insects, and found no statistically accountable difference in insect population numbers between Bt and non-Bt maize fields (Figure 4.4). By comparison, lowering of the insect population by a pesticide that bears the symbolic name of Karate is followed by recovery in some populations while others did not recover. Likewise, toxicological studies conducted with realistic quantities of the Bt toxin (Cry1Ab), and using appropriate statistical analyses, showed that even in the laboratory the larvae of green lacewings were unharmed. Thus, the signal to introduce this crop should be given, as we are now sufficiently informed about certain traits of Bt maize. Nonetheless, the situation may be different for other crops, and further research investigations should be conducted.

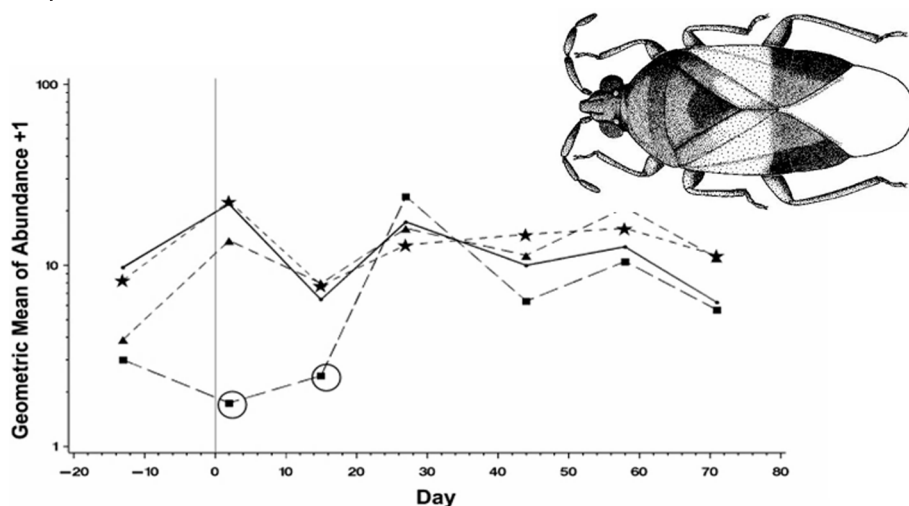


Figure 4.4 Population density of the *Orius* flower bug on maize fields planted with various crops. Circles: untransformed corn (control); stars: Bt-corn; triangles: untransformed corn treated with Delfin Bt biocide; squares: untransformed corn treated with Karate Xpress insecticide. Statistically significant effects are indicated by circling. (Source: Gandolfini et al., *Biocontrol Science and Technology* 14, 129–170, 2004).

4.3

Thesis 3: Re-think Communication

A re-think in communication schemes is clearly necessary. We do not communicate appropriately, especially in academic circles. The cartoon in Figure 4.5 symbolizes the academic situation, where the owls represent professors who must leave their ivory towers. There are also too many bench workers who have not yet realized that biology has lost its innocence and there is a social responsibility in proceeding with what is done. There is a difference between science and technology, and those people who develop the sciences should have a sense of responsibility about that. Unfortunately, this is often not the case. The solution would be not only to leave the ivory tower, but also to introduce a discursive model on communication where there is dialogue and respect for different types of knowledge.

Traditional knowledge cannot simply be looked down on with a neocolonial attitude. Much is hidden in traditional knowledge that may be discovered later by science. In medicine, for example, there is a huge wave of alternative medicine emerging from Europe and the United States, and more respect should be paid to different types of knowledge. If science is to be heard, then the debate should not be monopolized with scientific knowledge.

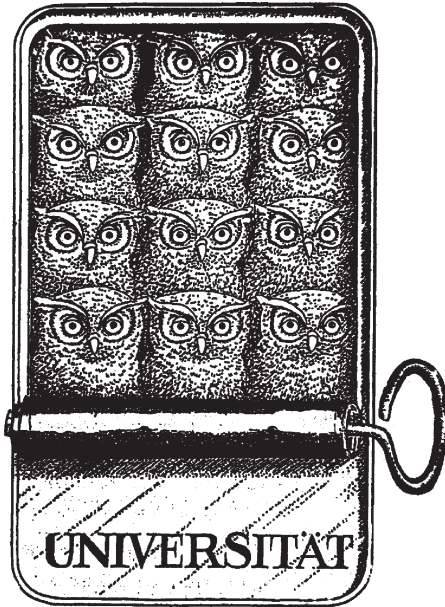


Figure 4.5 A cartoonist's view of scientists at the university.

Of course, scientific knowledge must be defended against scaremongers and organizations such as Greenpeace. Science alone cannot explain the whole world and its operations. There are culture, tradition and other hidden knowledge. People become nervous when faced with science alone, and confidence in science is at least harmed. But if the signal were to be given that scientists have respect for non-scientists, and that the latter are not seen as being fools, then the people will again listen to scientific arguments. The term “symmetry of ignorance” (or alternatively, the asymmetry of knowledge) is important, and today is to be found frequently among the professional literature relating to new management systems.

4.3.1

The Best Way to Solve a Problem

Only those people who are part of the problem should participate in finding a solution – there is no need to include highly paid moderators who know nothing of the issue. Such a proposal was made initially by Adam Kahane, a successful moderator who was involved in bitter fights after the abolition of apartheid in South Africa, but subsequently married a South African woman and so became part of the society. The naïve concept of the stakeholders is false for two reasons – first, it does not go into deep detail of the respect for different types of knowledge, and second, it does not follow Kahane’s solution.

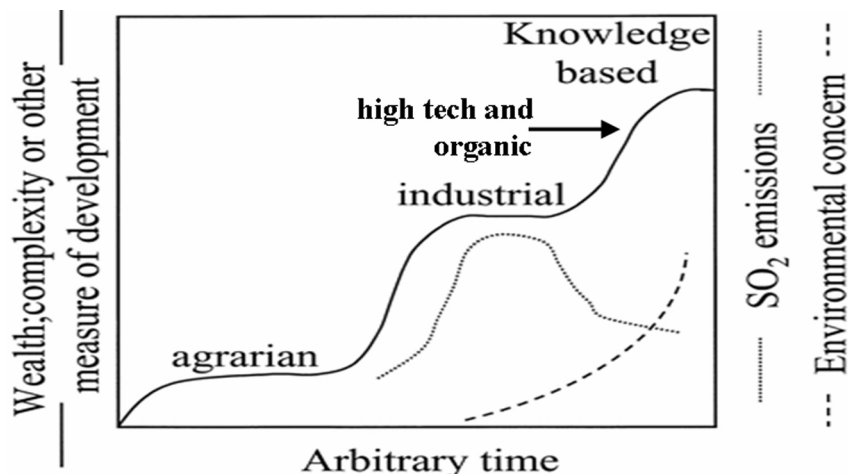


Figure 4.6 Relationship between economic development and environmental concern. The three primary economic systems of agrarian-, industrial-, and knowledge-based service are indicated with arbitrary indications of wealth and development. SO_2 emission is used merely as an indicator of industrial development and the subsequent environmental concern generated.

(Source: A. Trewavas, *Plant Physiology* 125, 174–179, 2001).

What are the implications for agriculture? The route to be taken is from the agrarian to the industrial to the knowledge-based agriculture (Figure 4.6). This must include both high-tech and organic farming, because in the discursive processes where those people who form part of the problem are involved there must be discussions with organic farmers. Of course, there will be believers and backward-thinkers among this group, but neither technology – whether organic or high-tech – is scale-dependent. Today, some huge organic farms operate very efficiently and successfully, while other much smaller farms carry out superb Bt cotton cultivation, so this is clearly not scale-dependent.

One excellent solution to our problems in agriculture is Golden Rice. The large quantities of vitamin A present in Golden Rice 2 were long-promised, and today there are clearly no problems related to its vitamin A content (Figure 4.7). While plant breeders are free from concern over this subject, the members of Greenpeace continue to worry. In fact, the Greenpeace website shows a slogan of mock Golden Rice which suggests that 9 kg of rice must be eaten in order to obtain sufficient vitamin A. This argument has now been deflated, however, with the development of Golden Rice 2. There is a more in-depth account of the Golden Rice story by Professor Potrykus in Chapter 5.

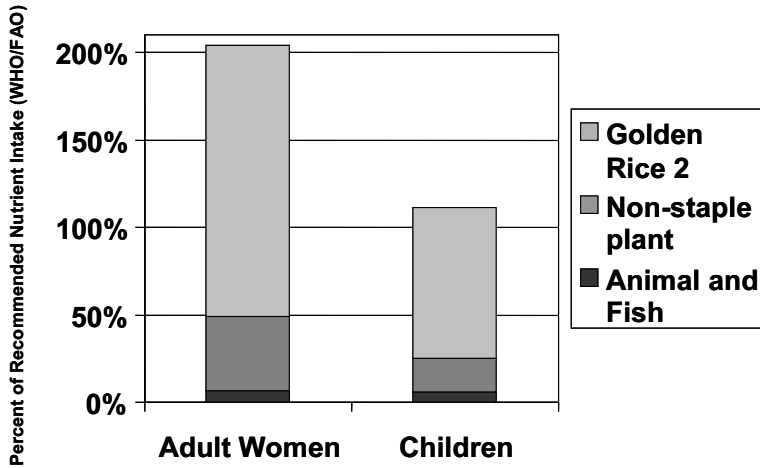


Figure 4.7 Contribution of Golden Rice 2 to nutrient intake. Data are from HarvestPlus (April 2005).

4.4

Thesis 4: Poverty Alleviation

There is no time left to conduct an ideological warfare on the alleviation of poverty, and advances must be made in a constructive and cohesive manner on these discursive processes. The chart developed by Swaminathan (Figure 4.8) illustrates the complexity of poverty alleviation, and it is really frightening to me as a botanist who is unaware of the elements of economics. Nonetheless, it is a complex battle that must be fought. The Millennium Project (which has recently been published and is also accessible on the Internet at www.unmillenniumproject.org) includes details of farm inputs including soil nutrients, reliable water for agriculture and improved seed varieties. It is the latter point in particular where plant breeding can contribute – in both transgenic and non-transgenic variations – together with vaccines, veterinary pharmaceuticals and feed and fodder for livestock.

By working together, much can be achieved. I had a wonderful encounter with my Amish friends who are actually my ancestors in the family. Jakob Ammann was the founder of the Amish and they got the name from him. When I start debating with Amish organic farmers about biotechnology, to my own bafflement, these farmers asked me to encourage Monsanto to offer them some transgenic vegetables and they have adopted partially the transgenic plants now. Organic farming does not have to be backward-looking and to be involved only in traditional systems. In the Netherlands, some farmers are producing lettuce strictly according to organic standards, and in a superb,

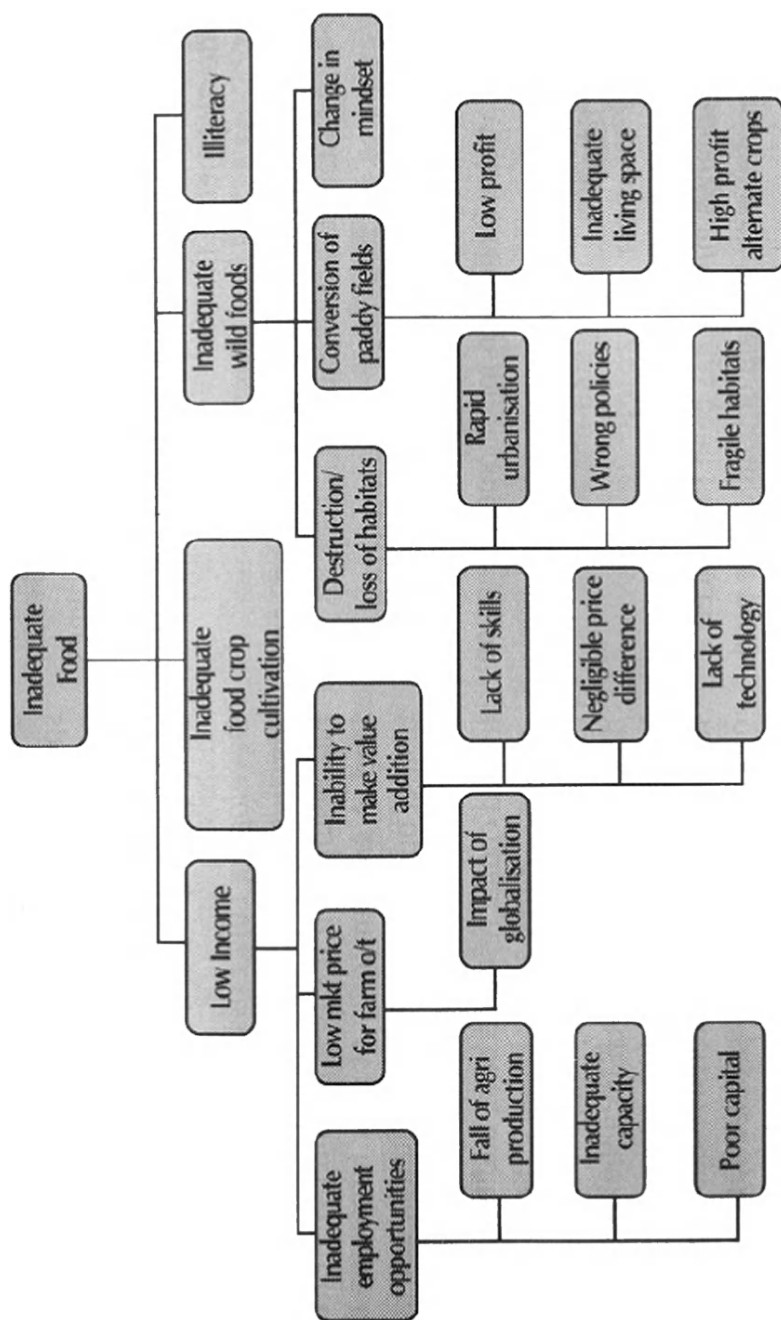


Figure 4.8 Swaminathan's view on tackling the problem of poverty in a highly complex system.



Figure 4.9 A Dutch farmer producing organic standard vegetables without pesticides. (Source: Weltwoche 06/2003).

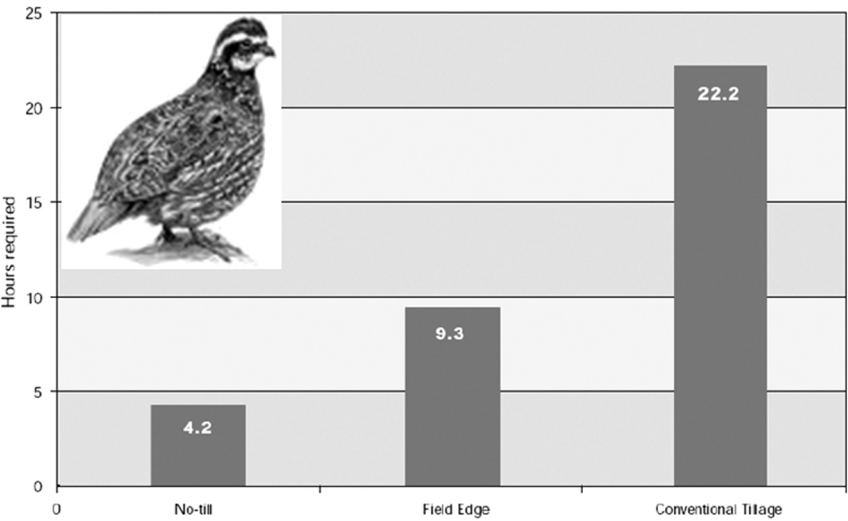


Figure 4.10 Time needed for Bobwhite quail chicks to satisfy daily insect requirements in a soybean field under different farming conditions. (Source: Fawcett and Towery, 2002).

modern, fully automated environment (Figure 4.9). It is important therefore, to remain open-minded – to take the best of organic farming and to combine this with high-tech processes. There is a clear need for organo-transgenic crops in the future, and this must be the target. In a modern untilled soybean field, for example, the bobwhite quail needs to feed for much shorter periods than on conventionally tilled fields (Figure 4.10), and in terms of soil fertility this suggests a trend towards organic farming. Likewise, the higher seed variety present on the untilled fields may be indicative of better ecology in soybean production.

4.5

Summary

In today's world, it may be more relevant to use the slogan "GenePeace" rather than Greenpeace, with scientists in Switzerland having recently demonstrated against the fundamentalists (Figure 4.11). The vote of the Swiss population was in favor of continuing a biotech approach by a two-thirds majority, and not only demonstrated the courage of those involved but also generated well-earned and much-needed publicity. The overall proposal, however, is that rather than conduct advanced research projects into what might have been, it is more intelligent and beneficial simply to "make peace" with organic or integrated farming. This is the available option, and that is the target. But of course the main point that must be remembered here is that, today, there are still 800 million hungry people in the world.



Figure 4.11 Swiss researchers demonstrate for more gene technology in agriculture.

Author Biography

Ingo Potrykus



*Professor Emeritus of Plant Sciences, Institute of Plant Sciences,
Swiss Federal Institute of Technology*

Ingo Potrykus was born 1933 in Hirschberg, Germany. He has studied Zoology, Botany, Genetics, Biochemistry, Philosophy, Physical Education at Universities in Cologne and Erlangen. He obtained a PhD in Plant Genetics 1968 at Max-Planck-Institute for Plant Breeding Research, Cologne, Germany; a degree in Botany 1982 at University of Basel, Switzerland. He was Asst. Professor, Institute of Plant Physiology, Stuttgart-Hohenheim from 1970–1974; Research Group Leader, Max-Planck-Institute for Genetics, Ladenburg-Heidelberg from 1974–1976; Research Group Leader, Friedrich Miescher-Institute, Basel, Switzerland from 1976–1986; Full Professor in Plant Sciences, Swiss Federal Institute of Technology (ETH), Zurich from 1986–1999.

He has made contributions to food security in developing countries, focusing on: development and application of genetic engineering technology for and to “food security” crops such as rice (*Oryza sativa*), wheat (*Triticum aestivum*), sorghum (*Sorghum bicolor*), and cassava (*Manihot esculenta*); problems difficult to solve with traditional techniques and in the areas of disease and pest resistance, improved food quality, improved yield, improved exploitation of natural resources, and improved bio-safety.

He has played a crucial role in developing and promoting “Golden Rice”, a sustainable contribution to reduce vitamin A-, iron-, and protein malnutrition, and 320 publications in refereed journals and 30 international patents. He has given lectures and courses in plant biology and plant biotechnology in the faculties of Biology, Agronomy, Pharmacy, Forestry, Environmental Sciences; International Training Courses for e.g. EMBO.

He received KUMHO (ISPMB) Science International Award in Plant Molecular Biology and Biotechnology 2000, the American Society of Plant Biologists

(ASPB) Leadership in Science Public Service Award 2001, Crop Science of America (CSSA) Klepper Endowment Lectureship 2001, CSSA President's Award 2002, European Culture Award in Science 2002, Honorary Doctor, Swedish University of Agricultural Sciences 2002.

He is a member of Academia Europaea, World Technology Network, Swiss Academy of Technical Sciences.

5

Is GMO Over-regulation Costing Lives?

Ingo Potrykus

5.1

Introduction

The immediate reply to this question is, yes – GMO over-regulation is indeed costing lives, is unjustified, is blocking product development in public goods R&D, and is preventing the solution of humanitarian problems.

In promoting scientific progress, it is invariably necessary to develop products that can subsequently be used within problem-solving schemes. And today, this approach is particularly relevant in the development of products utilizing genetically modified organisms (GMOs). Most people probably have no idea what it means to develop a GMO product, and in the following I will point out what I have learned over the last six years after my retirement when I had time to care for the problem of GMO deregulation.

5.2

Bio-fortification: Golden Rice

Golden Rice is characterized by the presence of activated genes that provide provitamin A in the polished grain, the development having been carried out in order to help overcome vitamin A deficiencies in rice-dependent populations. When these genes are active, the product differs visibly from normal rice (Figure 5.1). Golden Rice provides substantial amounts of dietary vitamin A, although a more recently developed variety, SGR-2, is superior to its predecessor in this respect.

This whole procedure is an example of a new concept termed “bio-fortification”, which means using the power of genetics to improve the nutritional

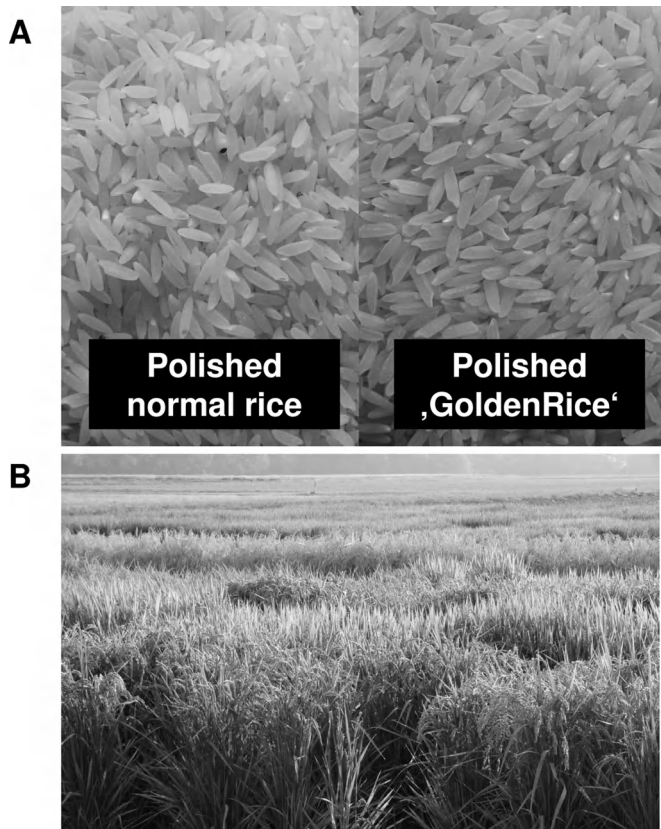


Figure 5.1 Golden Rice, a genetically engineered new rice variant rich in vitamin A.
 (A) Normal rice versus genetically engineered “Golden Rice”.
 (B) Field test with Golden Rice in Louisiana.

content of crop plants. Such a scheme is considered by institutions such as the International Food Policy Research Institute (IFPRI) to represent a sensible and intelligent approach towards reducing malnutrition, because it is both sustainable and very cost effective.

Golden Rice has been referred to by some as “Fools’ Gold”. Greenpeace, for example, suggested that it was a stupid scientific idea, as children would need to eat 9 kg of the rice each day to experience any beneficial effect. This should be seen as a mere propaganda statement.

In order to calculate exactly how much rice would need to be eaten, it is first necessary to identify what people are eating in general. Figure 5.2 illustrates IFPRI data from Bangladesh, where people eat not only rice but also other foods that they can afford, and some do not eat rice at all. People in Bangladesh derive about 79% of their dietary calories from rice (Figure 5.2A), which is

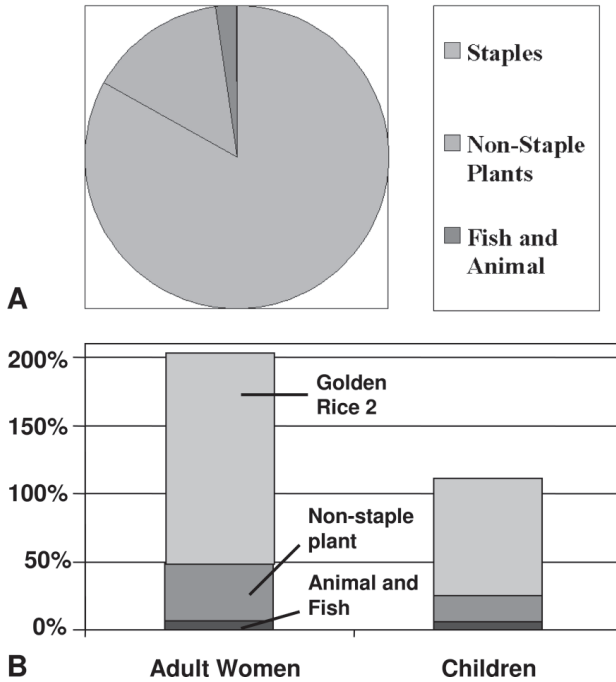


Figure 5.2 Contribution of rice to a typical rural diet in Bangladesh.

(A) Share of calorie intake.

(B) Share of vitamin A intake in percent of the WHO/FAO recommended daily allowance if Golden Rice replaced normal rice as the staple food.

(Source: International Food Policy Research Institute).

devoid of provitamin A. They also eat some vegetables and fruit, and some may eat a little fish and animal products, which will provide them with provitamin A. In Southeast Asia, rice contributes on average 40% of the energy intake; thus, vitamin A malnutrition is a major problem as dietary provitamin A intake is inadequate, such that the people are vitamin A-deficient. Golden Rice could prevent this vitamin A deficiency, at minimal cost, as indicated by Professor Ammann in Chapter 4.

The basic concept of bio-fortification to provide missing dietary ingredients is excellent. Recently, Golden Rice was field-tested, not in a developing country but in the United States, and did not indicate any agronomic or ecological problems. Moreover, the provitamin A content was higher in field-grown rice than in greenhouse-grown samples. In addition, a professional taste panel could not identify any negative taste or organoleptic problems with Golden Rice. The pathway to success for Golden Rice has been long, but by the end of 2005 it is envisaged that preliminary field tests will be undertaken in India and in the Philippines.

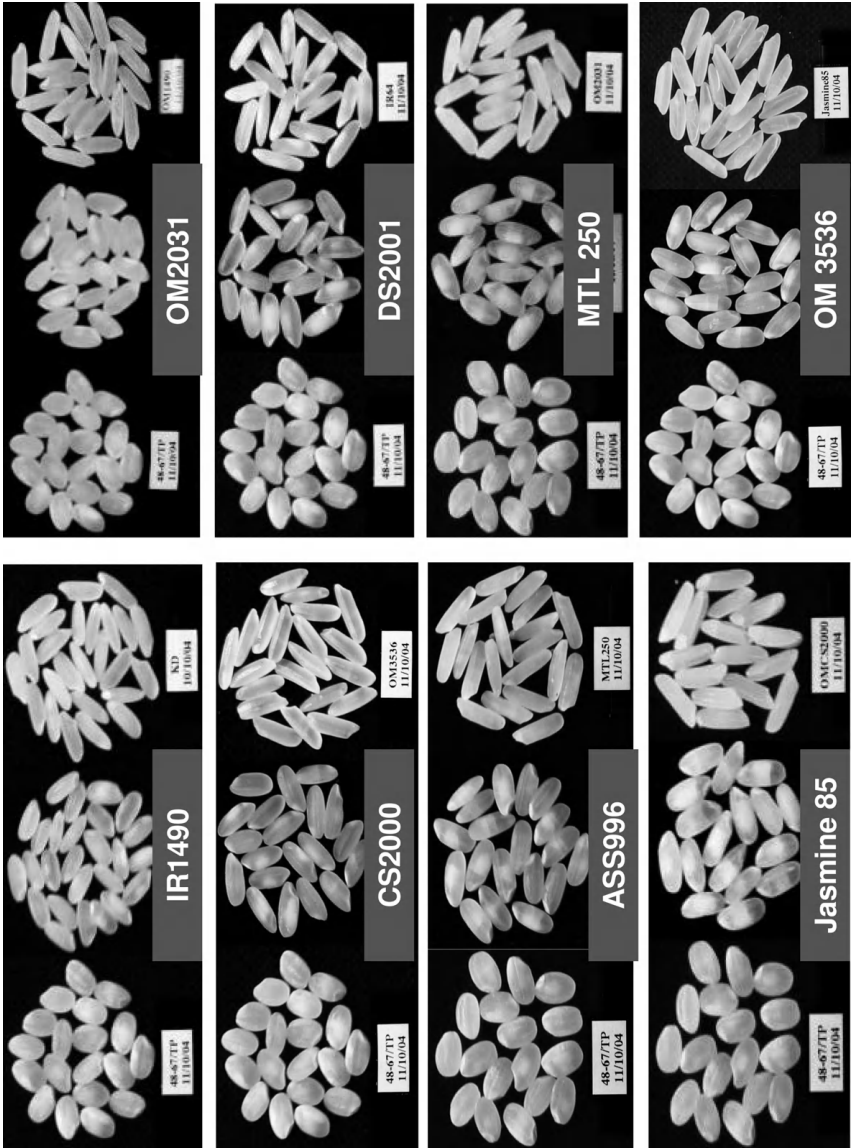


Figure 5.3 The “Golden Rice” trait has been transferred into numerous Southeast Asian rice varieties, including “high-iron”, “high-aromatic”, and “high-grain quality” varieties. (Source: Delta Rice Research Institute, Canton, Vietnam).

5.3

The Potential of Golden Rice

Genetic traits, as the one in Golden Rice, can be introgressed into other varieties, and this has formed the basis of the Golden Rice Humanitarian Network. Figure 5.3 shows some examples of Golden Rice from Vietnam, where Tran Thi Cuc Hoa, at the Cuu Long Delta Rice Research Institute, has introgressed the new trait, provitamin A, into a series of very popular local rice varieties. These varieties are high-iron, aromatic and high-grain quality, with the provitamin A trait being active in each case. In total, more than 40 local Southeast Asian varieties have been developed, including some from other members of the network. The problem is that although Golden Rice is capable of reducing death and blindness caused by vitamin A deficiency among the rice-dependent poor, its use has so far been prevented due to its GMO nature.

The potential impact of a single rice seed is impressive. One seed, when grown in the soil, will produce at least 1000 seeds in one generation. By repeating the process, a farmer would have one million seeds, or 20 kg of rice. Repeating again would provide 20 tons, and repeating again would provide 20 000 tons. This entire process would take only two years, but of course it would involve more than one farmer. Nonetheless, this equation states that from one seed, farmers could – in two years – produce sufficient rice to feed 100 000 people for one year. Moreover, by using Golden Rice, all of the seeds would contain the material needed to prevent vitamin A deficiency. The additional benefit is that the farmer would need neither additional agrochemicals, pesticides, novel farming systems, nor novel seed. He could then use part of his harvest for the next sowing, and could continue to do so to his children and grandchildren, *ad infinitum*. The final benefit is that this would be free of any costs and obligations, as long as the farmer makes a profit exceeding US\$ 10 000 each year. The reason for this final condition is that this technology has been targeted at subsistence farmers, and not for major industries. It is, therefore, justifiable to state that the concept of biofortification would provide an excellent and sustainable approach to the reduction of malnutrition.

5.4

GMO Over-regulation: Does it Cost Lives?

The question of whether GMO over-regulation is costing lives can also be explored in the context of Golden Rice. It is quite likely that if Golden Rice (which was developed in 1999) had not been a GMO, breeders would have developed new varieties within three years and farmers could have begun to use these from 2003 onwards. However, as Golden Rice is a GMO, it will take – even if everything runs smoothly – at least until 2009 to enter common use, which equates to a six-year delay. It should be remembered that, each day, 6000 children die from vitamin A deficiency, and that more than 50% of those would probably be dependent upon rice as their staple diet. So, assuming only 1% coverage for Golden Rice (official institutions assume a 10 to 50% coverage), delaying Golden Rice availability by six years due to GMO over-regulation could be deemed responsible for the deaths of $30 \times 365 \times 6 = 65\,700$ children.

It is difficult to see how such a situation could be justified by society, and one would expect that we have very good reasons to justify these extreme precautionary regulations for GMOs. With these data in mind, the question of why GMO regulation is required becomes paramount. There are historic reasons, because it was sensible (and reasonable) to take adequate precautions during the developmental stages of this technology. The key argument was – and still is – that the technique leads to unpredictable genome alterations. Yet despite 20 years' experience with this technology, together with 20 years' experience of deregulation, of biosafety research, and an ever-increasing knowledge of basic biology and plant breeding, there is still no clear proof of any specific risk associated with GMOs. Why, then, are such extreme precautionary regulations maintained? The argument is made that there is a need to build trust for the acceptance of GMOs. This seems to be a reasonable argument, but based on experience such trust has not been placed – and cannot be placed because any lay person will automatically assume that if something is so tightly regulated, then it must be very dangerous. No citizen wants to believe that the government would regulate something to such an extent that is, in fact, quite normal. So, to maintain extreme precautionary regulations achieves exactly the opposite effect.

The argument often put forward is that it cannot be said with total certainty that unintended alterations of the genome will not have any adverse effects. That is true, but this condition applies to all plant breeding processes, and in particular to everything eaten on Earth today. How then, can such extreme precautionary regulations be justified, especially when it involves the deaths of so many children?

5.5

Genome Alterations and Plant Breeding

In order to illustrate unpredictable genome alterations within plant breeding, it would help to examine the breeding tree leading to IR64, the most popular and famous rice variety on earth, which was produced by Gurdev Khush in the IRRI (Figure 5.4). The approach taken by plant breeders is to use landraces (shown as arrows in the figure). These are crossed to develop new varieties via subsequent selection. As new varieties have been developed (shown as dots), many crossing and subsequent selection procedures were passed on the way down to IR64, and many new varieties have been produced. There is not the slightest question that each step and each component in the breeding tree is leading to uncontrolled genome alterations.

To clarify this situation, Figure 5.5 shows the genome in addition to the breeding tree. The original rice genome is shown as an empty box in which bars appear during the course of the breeding process; the light bars depict mutations that are contributed by the landraces. Landraces differ one from another because they have different mutations. Mutations are, by definition, unpredictable and uncontrolled genome alterations. So, as the breeding process continues the subsequent selection leads to other, more dramatic alterations such as translocations, recombinations, inversions and deletions. By following the development of the IR64 genome, it is clear that it has been bred by using exclusively traditional methods, and is highly genetically modified. This is not an exception – it is true for all crop plant varieties used today. Hence, each variety of maize, wheat, cassava, apple or plum – whatever is being eaten – is highly genetically modified. Yet these are not referred to as being genetically modified products and are not so tightly regulated. From looking at their genomes, it is certainly very difficult to spot the difference between Golden IR64 and IR64. This is a precise additional modification, and it is even more difficult to understand why this rice has been altered in such a way that it cannot be used. There is clearly no logic to this situation.

5.6

Rational Regulation

There is no scientific basis for specific GMO regulations, and this is confirmed by the multitude of biosafety research conducted, especially in Europe. Likewise, many reviews and scientific publications have been prepared on the applications of GMO crops. It is, therefore, nonsense to maintain the present extreme precautionary regulation at the cost of so many lives. Society has a clear duty to establish a rational regulation system that includes the evaluation of benefits, and to apply it using common sense. The present system ignores benefits; rather, it is obsessed with hypothetical risks and is simply an opportunistic response to anti-GMO activists or political pressure. This situation should not be accepted.

The question of rational regulation is simple, if common sense is applied. In order to deregulate Golden Rice, the first point to determine is what is “novel”. With Golden Rice, the novelty is that there are carotenes in the endosperm. But in fact, the entire rice plant is filled with carotenes, which are eaten daily and are beneficial, rather than harmful. Any fear that carotenes in the endosperm might have a negative effect on the environment is unwarranted, because there is no real basis for any selective advantage in any environment, and if a character does not offer a selective advantage it cannot be maintained or sustained within the environment. Hence, there is no risk and there should be no restriction for testing Golden Rice in the field. In reality, however, the battle to test Golden Rice under very restricted conditions in the field has been continuing for four years, without success. Again, this situation is both insensible and illogical.

Next then is the questions of potential effects on the consumer of Golden Rice. While there is the clear positive effect for the consumer in that it can reduce vitamin A-based malnutrition, there may also be possible negative effects that demand attention. The question here is whether there are any unintended products that could cause problems – and again, the answer is simply, no. The mechanism behind Golden Rice is simply to activate the natural pathway of carotenoid formation, without forming any unwanted by-products, and this has been thoroughly investigated. Consequently Golden Rice should be released immediately for an unrestricted development of varieties and for immediate use by local farmers. The summary of this reasoning relates back to a recommendation of the US Academy of Sciences some 12 years ago when, after lengthy discussions about the problem of GMOs, the academy pronounced that it made sense to regulate the trait, but not the technology. The request must be made, therefore, that common sense should also be used when assessing these issues.

The message put forth by many is that GMOs are risky to eat, yet a recent study which examined Food-Related Illness and Death in the United States

Table 5.1 Food-related illness and death in the United States in 2002.
(Source: P. Mead et al., Centers for Disease Control and Prevention,
Atlanta, Georgia, USA).

<i>Known pathogens; non-gastroenteritis</i>	<i>Known pathogens; acute gastroenteritis</i>	<i>Unknown agents; acute gastroenteritis</i>	<i>GMO-derived health problems</i>
Illness 120 000	Illness 14 000 000	Illness 62 000 000	Illness 0
Hospitalization 5000	Hospitalization 55 000	Hospitalization 263 000	Hospitalization 0
Deaths 900	Deaths 900	Deaths 3400	Deaths 0
Total illness 76 000 000	Total hospitalization 323 000	Total deaths 5200	Total GMO-derived 0

in the year 2002 puts these suggestions into perspective. The data showed that, among 76 million cases of illness, 323 000 cases of hospitalization and 5200 deaths, there was not a single case of illness or hospitalization or death related to GMO-derived products (Table 5.1). Clearly, it is not GMOs that pose problems for health – rather it is the trend towards organic foods which may lead to a rise in food-borne illness.

5.7

The Effect of GMO Over-regulation

The deregulation of GMOs involves a number of requirements from extreme precautionary evaluations (Table 5.2). There are many requests, and the experiments to justify them must be conducted in a way that the data submitted are of scientific publication quality. This means that the process must start with a specific GMO product development requirement – to start with an event and then develop a product is unacceptable. In addition, the requirements of the deregulatory procedure must be considered when starting to develop a GMO product; this means that regulatory-clean technology must be employed until a regulatory-clean event is identified that can form the basis for product development that might pass through the regulatory process. Generally, this process involves four to eight years of intensive experimental studies, with no chance of publishing any findings, and with great problems of financing. If and when such an event is identified, work can begin towards deregulation. This means a further five years of intensive experimental studies, again without publication and with financial problems.

Table 5.2 Requirements for Golden Rice deregulation.

<i>Event-independent studies</i>	<i>Event-dependent studies</i>
Exposure evaluation Modelling analysis for intended use. Bioavailability study.	Molecular characterization and genetic stability Single copy effect; marker gene at some locus. Simple integration; Mendelian inheritance over three generations (minimum). No potential gene disruption. No unknown open reading frames. No DNA transfer beyond borders. No antibiotic resistance gene or origin of replication. Insert limited to the minimum necessary. Insert plus flanking plant genome sequenced. Phenotypic evidence for stability over 3 generations. Biochemical evidence for stability. Unique DNA identifier for traceability/detection.
Protein production and equivalence Extraction from GMO plant or heterologous source. Biochemical characterization. Function/specificity/ mode of action.	Expression profiling Gene expression levels at key growth stages. Evidence for seed-specific expression.
Protein evaluation No homology with toxins and allergens. Rapid degradation in gastric/intestinal studies. Heat lability. No indication of acute toxicity in rodents. Further allergenicity assessments (Daffodill).	Phenotype analysis Field performance, typical agronomic traits, yield – compared to isogenic lines. Pest and disease status to be same as isogenic background.
	Compositional analysis Data from 2 seasons × 6 locations × 3 reps. on proximates, macro and micro nutrients, antinutrients, inherent toxins and allergens. Data generated on modified and isogenic background.
	Environmental risk assessment Minimize potential for gene flow. Evaluate any change in insect preference – by field survey.

What does this mean for public goods research? No scientist or institution in the public sector has the expertise, the capacity, or the financial resources to develop a GMO product, nor can he or she afford to spend a decade on product development and the deregulation of a single transgenic event. The consequence is that present GMO regulations prevent the development of products by the public sector that might solve humanitarian problems. And it is the public sector – not the private sector – which is responsible for solving humanitarian problems.

The illustration in Figure 5.6 shows that progress in plant biotechnology has been very impressive, although the fact should not be overlooked that

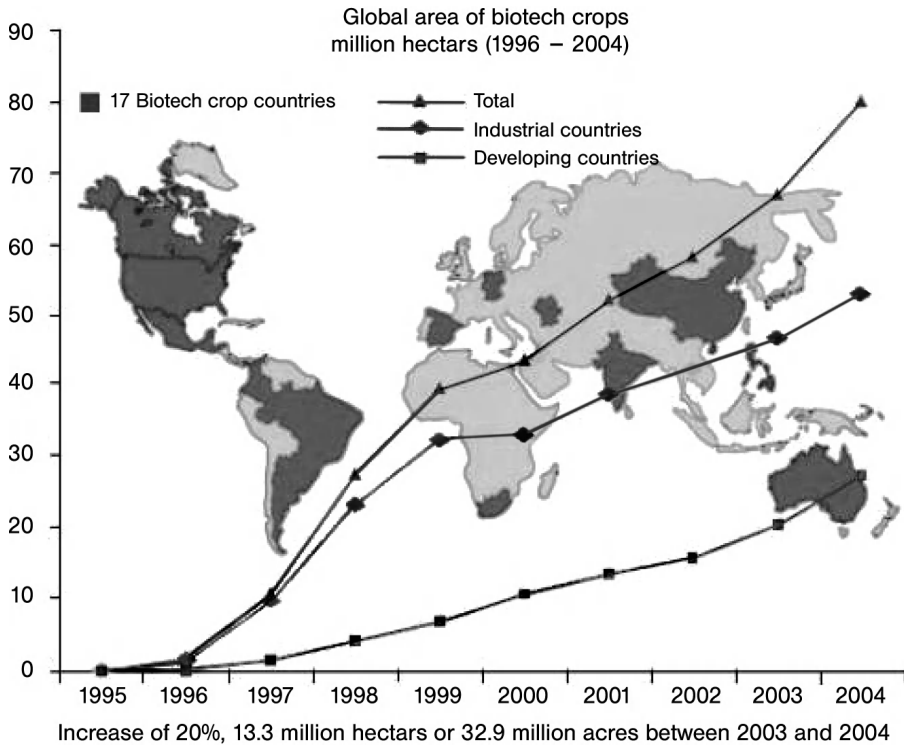


Figure 5.6 Increase in the global area farmed with biotech crops.
(Source: C. Williams, ISAAA, 2005).

this advance is based on only two traits and four species of GMOs, all of which have been developed and deregulated in the United States by the private sector, and subsequently adopted by developing countries. These crops include cotton, maize, soybean and canola with herbicide tolerance and insect resistance. Novel GMO cases from the public sector have little chance to contribute to this situation in the near future if the current standards of regulation are maintained.

So, the question must be asked again – is GMO over-regulation costing lives? Today, hundreds of food-security transformation events are produced in the public domain, for example in Egypt, Kenya, South Africa, Zimbabwe, China and India. These are conducted in rice, maize, pearl millets, sorghum, wheat, potatoes and cassava, each with improved agronomic performance, stress tolerance and nutritional value – and all are faced with the same prohibitory regulation as Golden Rice. As a consequence, the number of deaths due to GMO over-regulation will extend into the hundreds of thousands. But it is not only Golden Rice which is under pressure – there are very many

other cases in the pipeline in the public sector which have been blocked. Nonetheless, science is moving ahead towards nutrition optimization and the prevention of malnutrition due to provitamin, iron, zinc and protein. In this respect, investigations are continuing towards the development of rice with high contents of iron, zinc, vitamin E and protein. Sadly, it is very clear that none of this will reach poor farmers because it will be stopped by deregulation.

Fortunately, however, there are two international programs which use both molecular and traditional technologies to realize this concept of biofortification. With support from the World Bank, the National Institutes of Health and the Gates Foundation, these programs hope to produce not only biofortified rice but also bio-fortified sorghum, cassava, potato, banana, maize, wheat, sweet potato and beans. There is no doubt that, in five to ten years' time, there will be high-iron, high-zinc, high-provitamin A and high-quality protein rice, sorghum, cassava and potato available, and this will form the basis for a sustained reduction of malnutrition in general.

Although the question of GMO over-regulation costing lives has still not been confirmed, it is known that iron deficiency affects three billion people, zinc deficiency one billion, and essential amino acid deficiency 500 million. In most cases, the deficiency will extend to more than one micronutrient. For each single trait the present regulations will have similar disastrous consequences as for Golden Rice. Of course, multiple traits would provide the ideal means of fighting malnutrition, but they could probably never be deregulated following current standards. Consequently, it is fair to say that in time GMO over-regulation will indeed cost many millions of deaths.

5.8

Summary

And finally, an anecdote. A 19th century Thai princess, while celebrating her 18th birthday, fell into the palace pond and drowned in front of hundreds of guests. Nobody attempted to rescue her because it was taboo to touch a royal family member. However, everybody likes to believe that they would have rescued her, if they had been present. In the 21st century, each year 500 000 children become blind, while each day 6000 die from vitamin A malnutrition. This too could be prevented. The techniques are known, but GMOs are so over-regulated that they cannot be used.

Here is my final statement. GMOs are not demons, they are totally normal plants. Our society has a responsibility for de-demonizing GMOs. If this cannot be achieved, then history will – quite rightly – hold us responsible for a crime against humanity.

Author Biography

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Rafael Rangel-Aldao is Director of Research and Innovation of Empresas Polar, the largest food and beverage conglomerate of Venezuela and the third of Latin America. He has published extensively with scientific and technological contributions in a wide range of fields encompassing biochemistry, molecular biology, chemistry, plant physiology, and medicine, to food product development, industrial processes, and agricultural research in marker-assisted plant breeding. R. Rangel-Aldao is author of several families of international patents in biotechnology, genetic engineering, and chemistry applied to both the food industry and molecular medicine. He reports to the CEO of Empresas Polar for all the research and innovation of three major business units, Foods, Beer, and Soft drinks and Functional Beverages (a JV with Pepsico). To accomplish his duties, he directs two private centers of research and development, the Polar Technology Center in Caracas (Foods & Beverages) and Foundation DANAC (Plant Breeding) in San Javier, Yaracuy State. He is the founder and member of the Steering Committee of the International Consortium for Research and Development on Beer Flavor Stability, together with the Carlsberg Research Center in Copenhagen, and Heineken Technical Services in Zoeterwoude, Holland. Concurrent with his position in industry, R. Rangel-Aldao has been for more than twenty-five years a professor of molecular biology, biotechnology, and biochemistry at Simón Bolívar University, and at the Institute of Advanced Studies, both in Caracas, Venezuela. Born in Caracas, he received his degree in Medicine at University Central of Venezuela (M.D.), and of Doctor of Philosophy (Ph.D.) at the Department of Molecular Biology, Albert Einstein College of Medicine, New York. He has received numerous awards and prizes, is a member of several scientific societies, visiting professor at Yale, Université de Lovain, Universidade de Sao Paulo, Catholic of Chile, and Arizona State

University. He is or has been a member of the editorial board of Biological Research, Electronic Journal of Biotechnology, and Revista Colombiana de Biotecnología, as well as a writer of scientific journalism, activity that has rewarded him with several prizes. He is a frequent speaker at universities and companies of the USA, European Union, and Latin American countries, as well as consultant in biotechnology issues for WIPO, UNIDO, WHO, UNDP, and several Governments of Latin America. Fluent in 5 languages, as a writer he has finished Janus Web, his first novel on the social impact of science on democracy.

6

How to Make the Global Food Marketplace Work Better

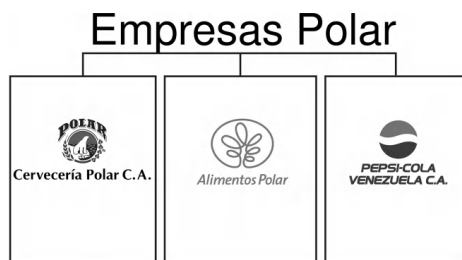
Rafael Rangel-Aldao

6.1

Introduction

In this chapter I will focus mainly on the global food marketplace, and rely heavily on two recent reports of the Food and Agriculture Organization (FAO). My approach will be to present maps of how the components of the marketplace interact, and ultimately attempt to identify the cause and effect of these components.

By way of introduction, my company – Empresas Polar – comprises three major business units: the production of beer (Cerveceria Polar), foods (Alimentos Polar), and a joint venture with Pepsi. The company employs some 20 000 people, and has annual sales of US\$ 3 billion in different countries of Latin America. Notably, the company has a Director of Research and Innovation, who reports to the CEO. There is also a joint venture with Frito Lay, which provides exposure through different countries of Latin America. Recently, the company has made huge investments in Venezuela, contributing 2.9% of non-oil fiscal revenues and 1.4% of the national labor force, employing almost 20 000 people (Figure 6.1).



Contribution to the 2004 Venezuelan Economy

- **2.90 %** of Non Oil Fiscal Revenues
- **1.4 %** of the National Labor Force
- Currently employing **19,000** people directly and **150,000** indirectly

Figure 6.1 The company Empresas Polar.

6.2

The Food Global Marketplace

The so-called food global marketplace can be divided into food supply, food demand, and market forces. In the case of demand, in today's world there are two billion people who are affluent, two billion people in transition, and another two billion at risk (Figure 6.2). Today, approximately 100 million people have a daily income of less than US\$ 1. One factor that would cause the global food marketplace to function better would be that of trade. Thus, the subject of global trade, self-organization and self-regulation by using network theory, will form the basis of this section.

The affluent population has a diet of high calories and cheap foods, and demands large quantities of grain. This is also an aging population, but with a trend towards "wellness". In considering the population at risk, both malnutrition and poor education are apparent, and the people will live an urban rather than a rural environment. The emergence of perhaps 14 megacities, each comprising more than 50 million people, creates another difficulty of how to feed the people because there is a major problem of distribution. With regard to self-regulation of the system, there is good news, and in terms of numbers of undernourished people good progress has been made in recent years (Figures 6.3 to 6.5). Another characteristic of these at-risk people is that they are net importers, there being clear differences in this respect between developed countries and developing countries (Figure 6.6).

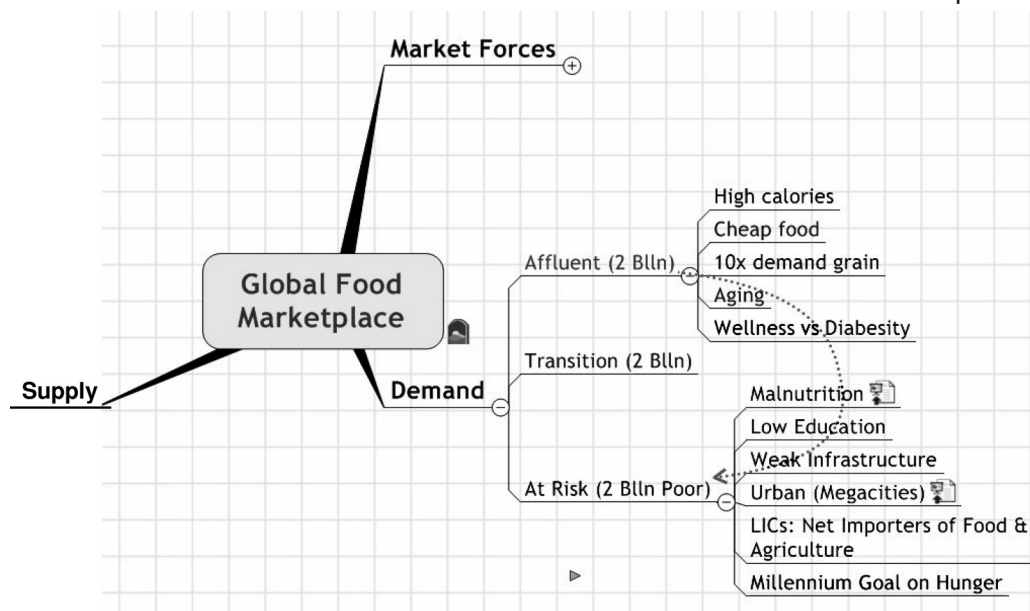


Figure 6.2 The global food marketplace map. (1) Demand.

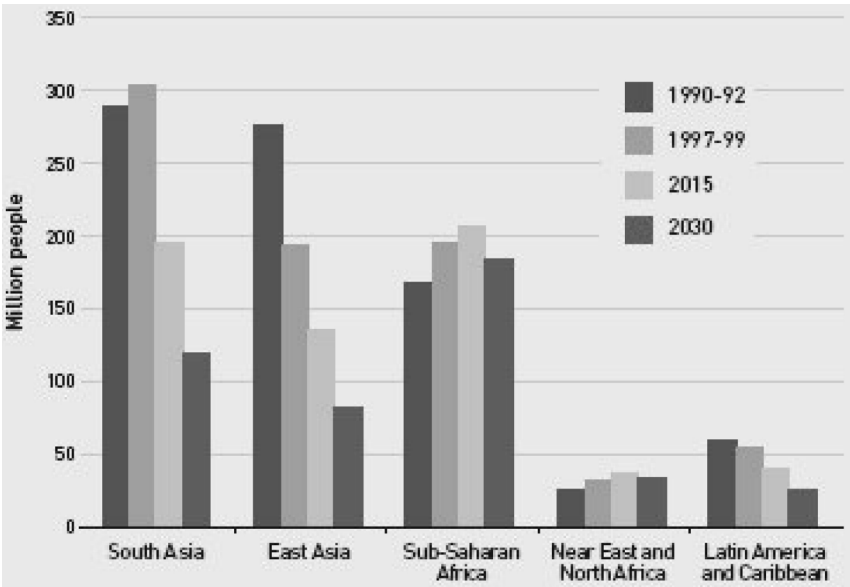


Figure 6.3 Numbers of undernourished people, by region.
(Source: FAO data and projections).

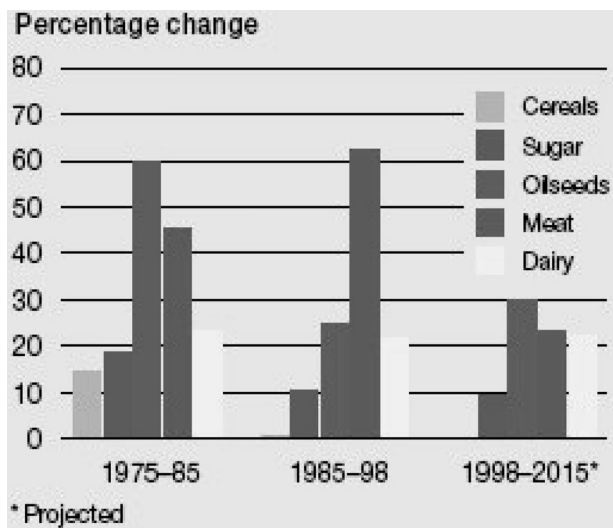


Figure 6.4 Changes in per capita food consumption in developing countries. The consumption of meat, oils, and dairy products has increased rapidly, but that of cereals has not. (Source: FAO).

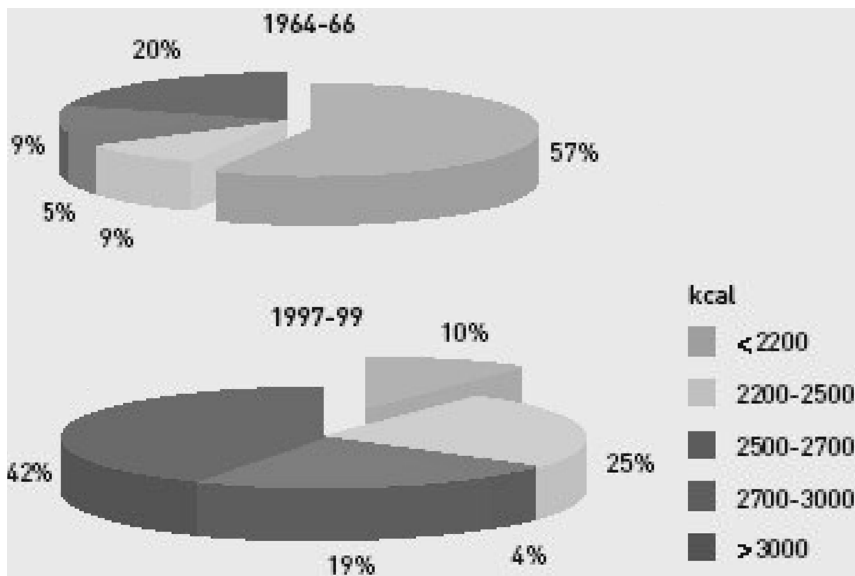


Figure 6.5 Global progress in nutrition: Energy intake levels by percentage of the world's population. (Source: FAO).

	Export shares 1999–2001				Import shares 1999–2001			
	Least developed countries	Other developing countries	Transition countries	Developed countries	Least developed countries	Other developing countries	Transition countries	Developed countries
Cereals	5	11	19	16	40	27	12	8
Oilcrops	14	26	16	14	24	24	15	15
Meat	1	9	15	21	4	9	14	20
Dairy	0	1	11	11	5	7	4	8
Sugar	4	7	3	3	9	5	11	2
Horticulture	4	15	6	14	2	6	13	20
Tropical beverages	28	15	7	7	3	4	12	13
Raw materials	43	16	25	15	13	19	19	13
All agricultural	100	100	100	100	100	100	100	100

Figure 6.6 The state of agricultural commodity markets. (Data are from 2004).

6.3

Market Supply

With regard to market supply, there are two main components – global production and trade. Currently, trade is falling in the least developed countries, and there is a clear asymmetry in terms of trade for agriculture. Thus, since 1986 the least-developed countries have moved from a net trade surplus to a net deficit, and consequently there will be net food importers within these least developed countries (Figures 6.7 and 6.8). Today, 48 of 63 low-income countries are net food importers, whilst only 15 are net food exporters. Unfortunately, these net food importers create another problem for the future because the people will be more dependent upon imports. Fortunately, the prices have been falling.

In the case of global production (Figure 6.9), the relevant technologies are available, but on occasion these may not be applied because of the GMO regulations. Rice yields grew at an average of 2.3% per year between 1961 and 1989, but were seen to slow markedly during the 1990s, falling by more than half to 1.1% between 1989 and 1999. A similar situation was apparent for wheat (Figure 6.10). Clearly, the yields are insufficient to satisfy the needs. There is also the issue of exhausting the natural resources of land and water in some parts of the world (Figure 6.11).

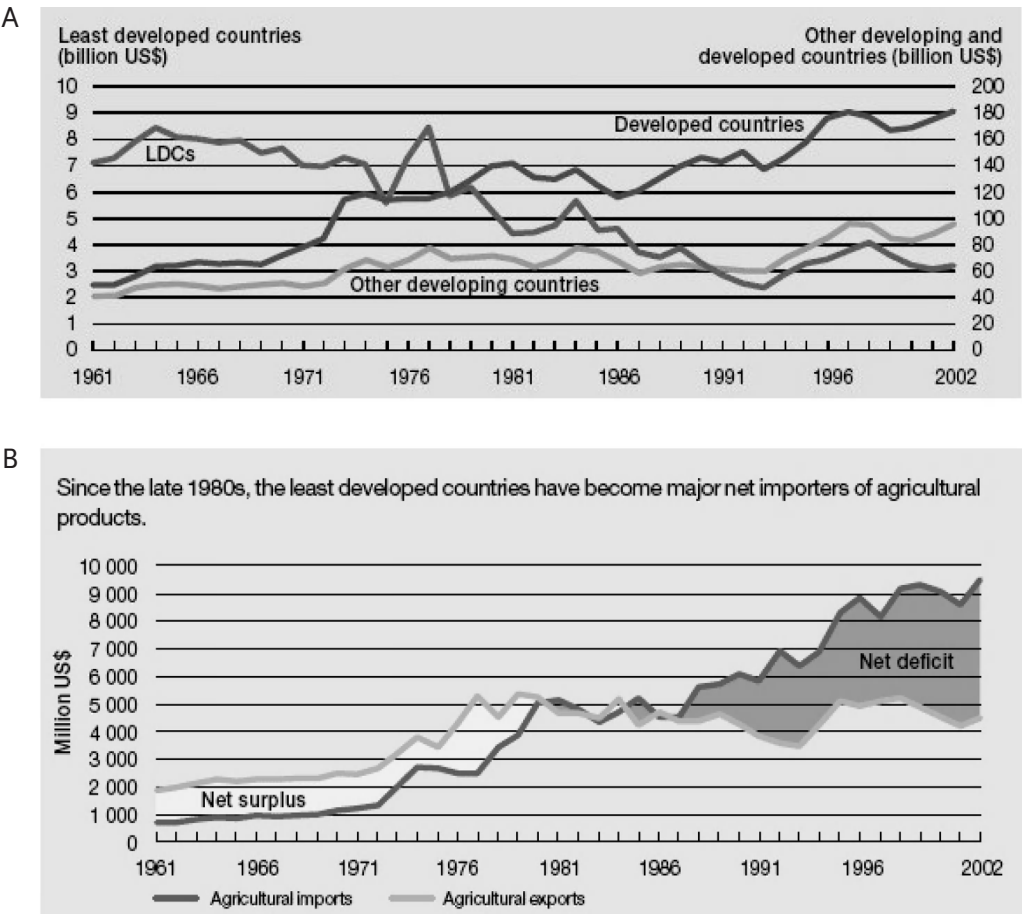


Figure 6.7 Global trade in agriculture.
(A) Trade income from agricultural exports.
(B) Agricultural trade balance in the least-developed countries.
(Source: FAO).

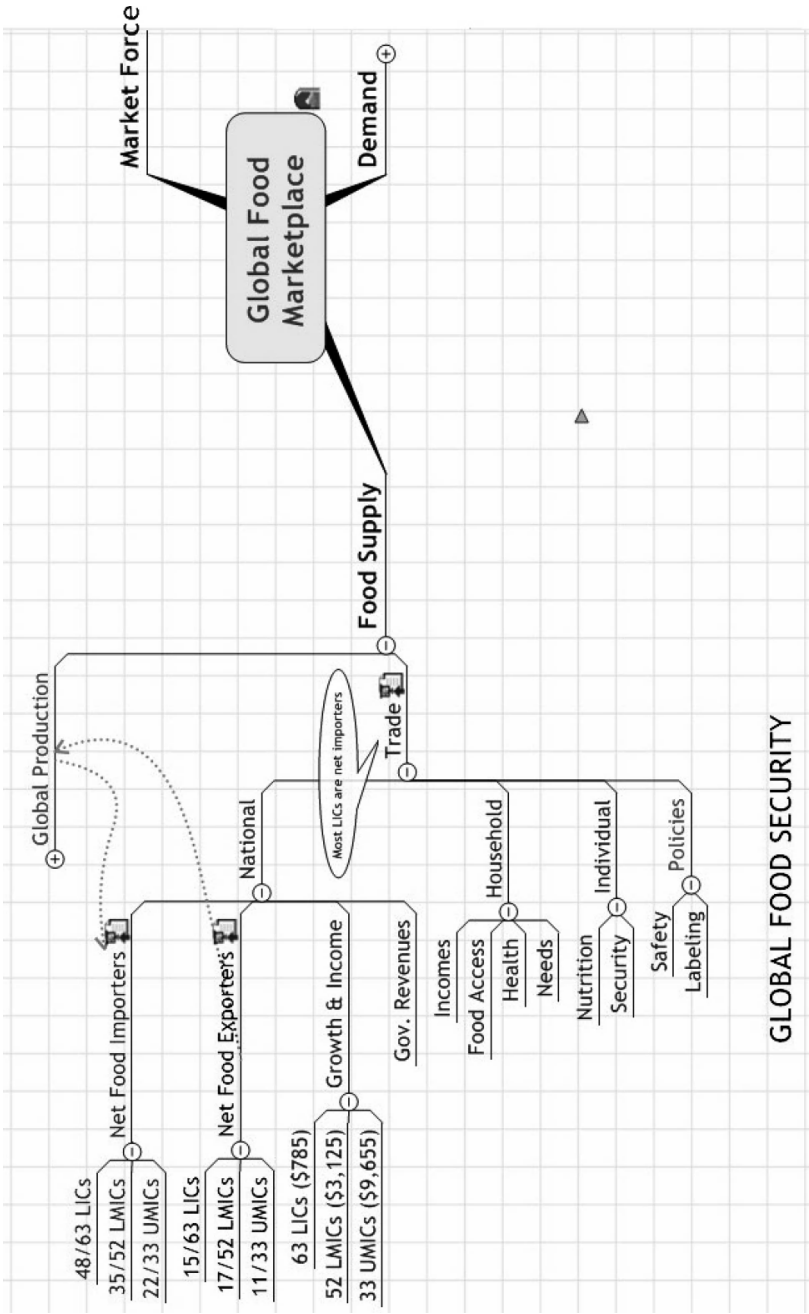


Figure 6.8 The global food marketplace map. (2) Trade.

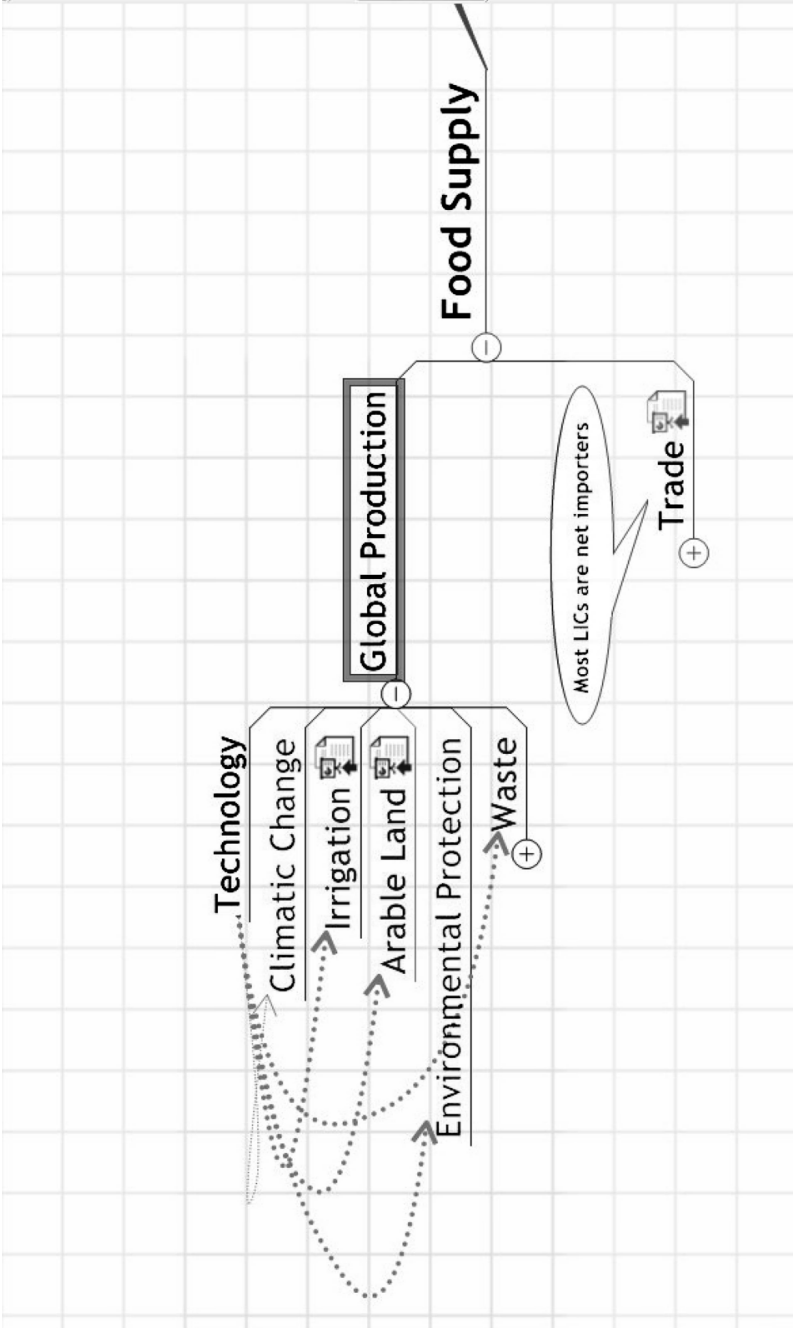


Figure 6.9 The global food marketplace map. (3) Global production.

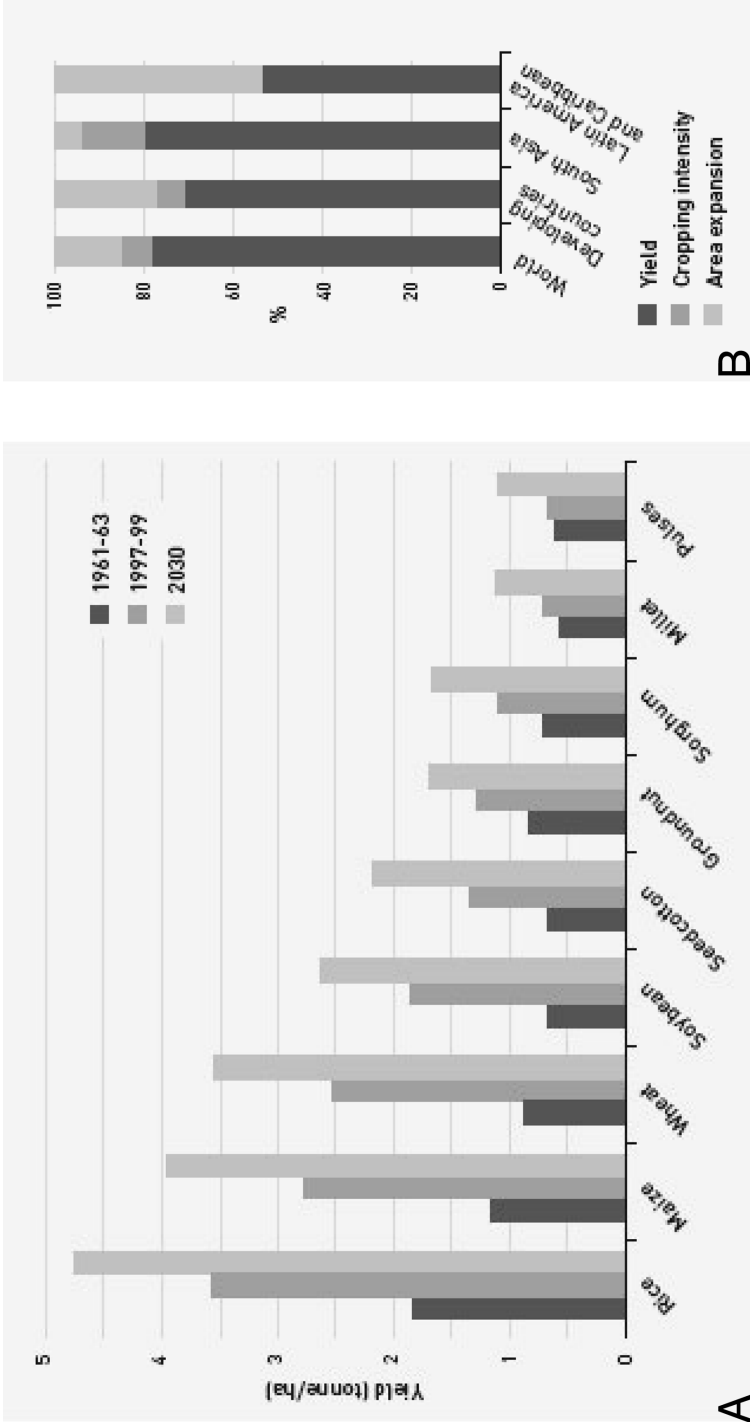


Figure 6.10 Global growth in agricultural production. (A) Crop yields in developing countries. (B) Sources of growth in global production. (Source: FAO).

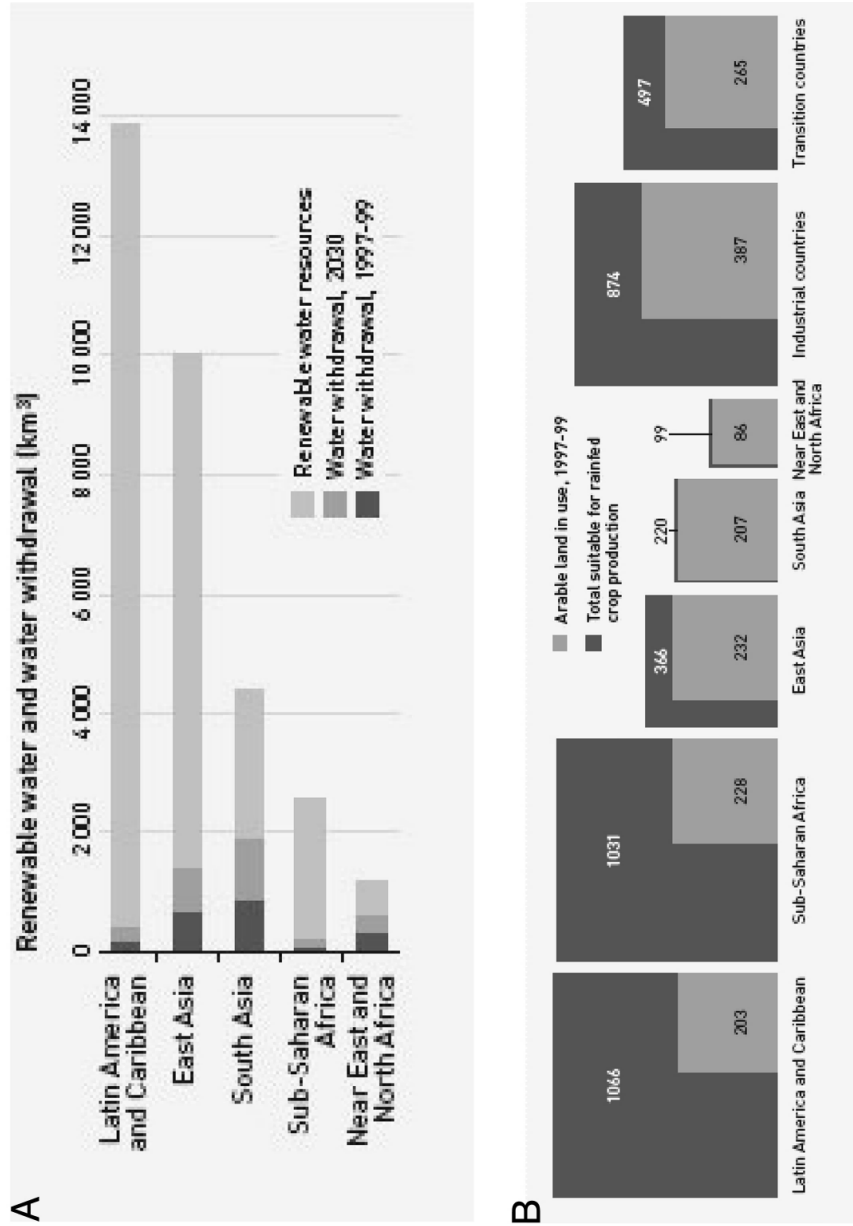


Figure 6.11
Natural resources for agriculture.
(A) Irrigation and water resources. (B) Arable land (in million hectares).
(Source: FAO data and Fischer et al., 2000).

6.4

Market Forces

Market forces are those forces that create profits from the global food marketplace, there being trends that modify the distribution of profits among those groups that form the value creation chain. These groups include food processing, which takes the lion's share of the profits (47%), retailing (24%) and food service (16%), whilst farmers and agribusinesses receive only 13% (Figure 6.12). Still, the discussion often becomes centered on only the farmers and their business. Among the food production and food processing companies are two major competitors, Nestlé and Unilever (Figure 6.13). One very interesting phenomenon seen in US food manufacturing is the product concentration ratios identified among the beef packers, grain terminals, corn exporters, flour milling and soybean crushing (Figure 6.14). For retailing, and especially for hypermarkets, there has been a global expansion of the five largest transnational food retailers. Another new phenomenon is that of hard discount stores; in Latin America this type of store allows people to purchase more food because they offer discounts of 30–40%.

In the US, there is a huge concentration in food retailing, with supermarkets accounting for about 80% of all food sales (Figure 6.15). The basic situation here is one of consolidation, whereby a few companies control almost everything.

An attempt to explain the use of a network theory can be made by examining the food service. At the level of farmers and agribusinesses, discussions have been conducted with regard to protectionism, tariff barriers and domestic support (Figure 6.16). The FAO data illustrated in Figure 6.17 indicate the effect of tariffs on trade. Export subsidies (Figures 6.18 and 6.19) and domestic support serve as huge barriers for free trade in the world. In the case of low- to middle-income countries, the good news is that market integration is occurring and, following the establishment of the World Trade Organization (WTO), this integration has accelerated (Figures 6.20 and 6.21). The good thing about this integration is that it is creating ground rules for trade and for the integration of these markets. In the case of agrochemicals, there is clearly consolidation, with the top 10 companies having 84% of the US\$ 334 billion of exchange (Figure 6.16).

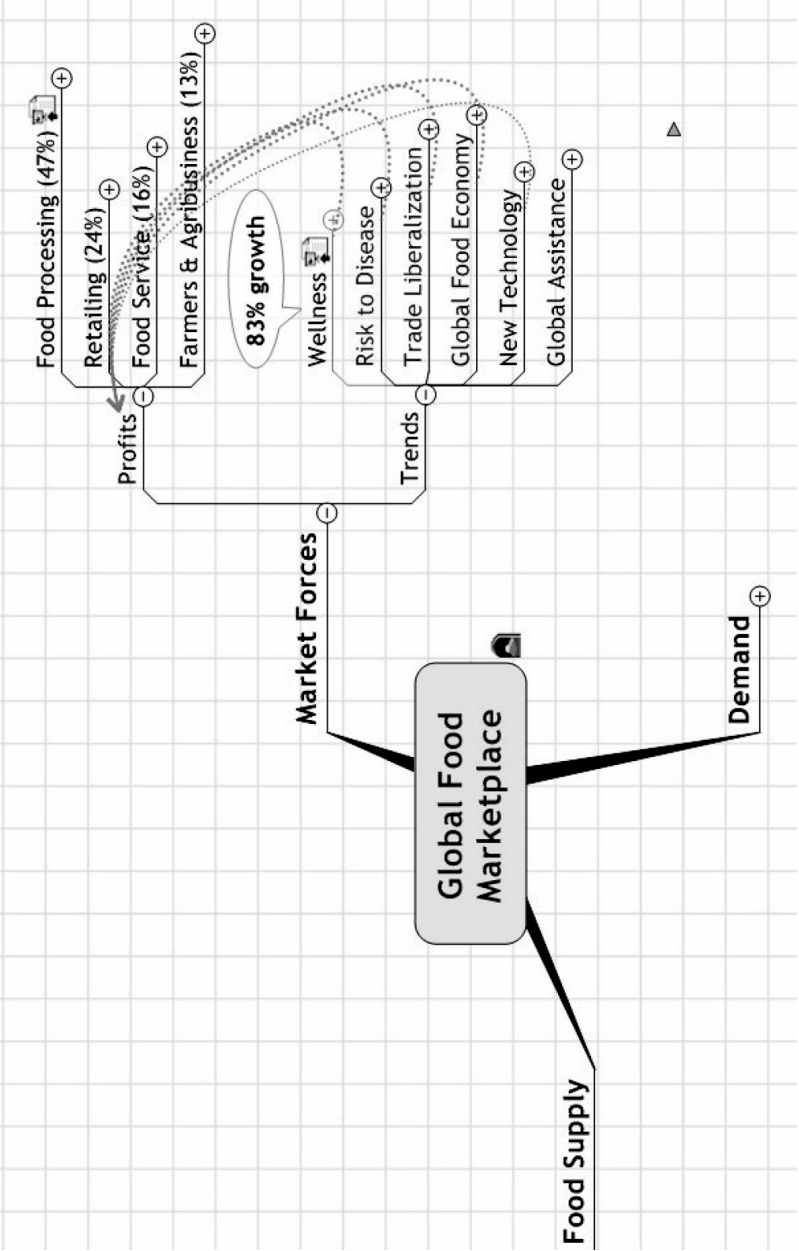


Figure 6.12 The global food marketplace map. (4) Market forces.

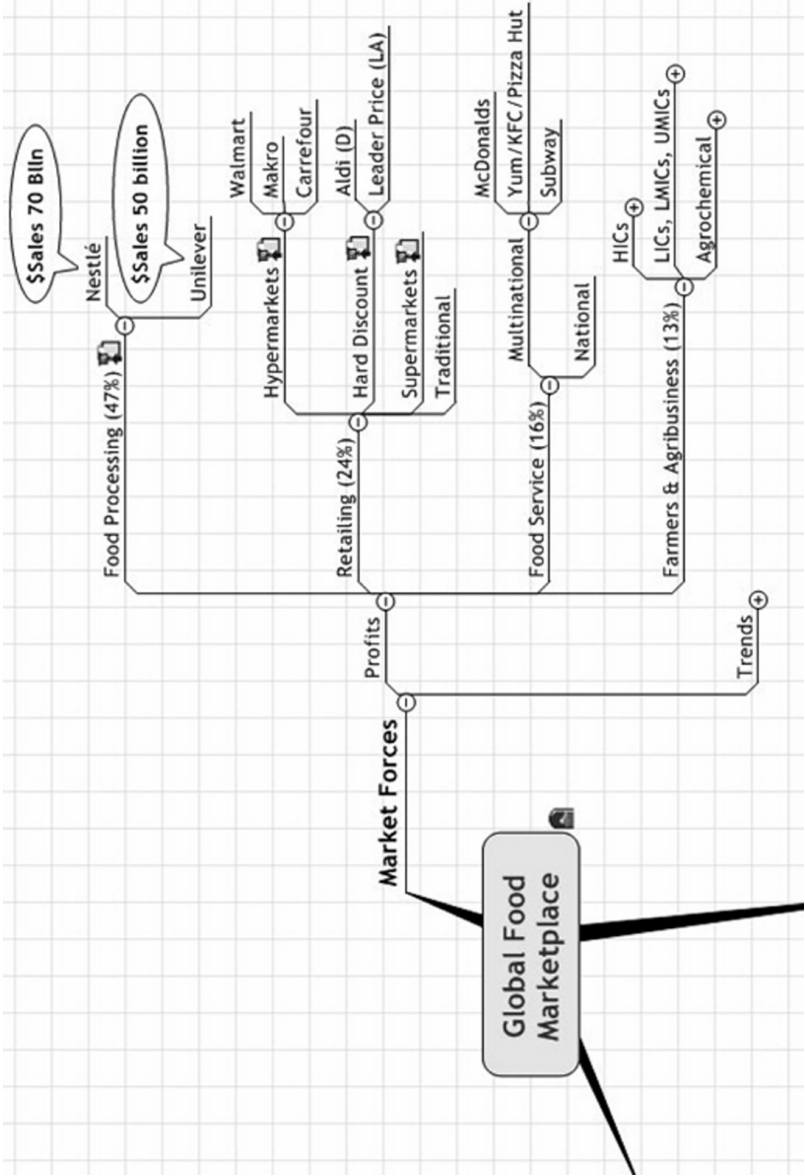


Figure 6.13 The global food marketplace map. (5) Profits.

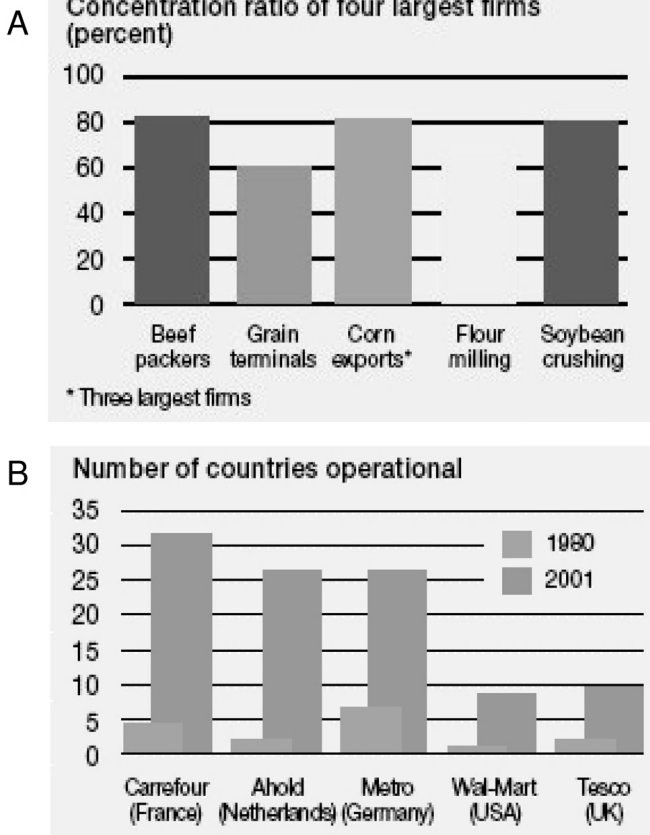
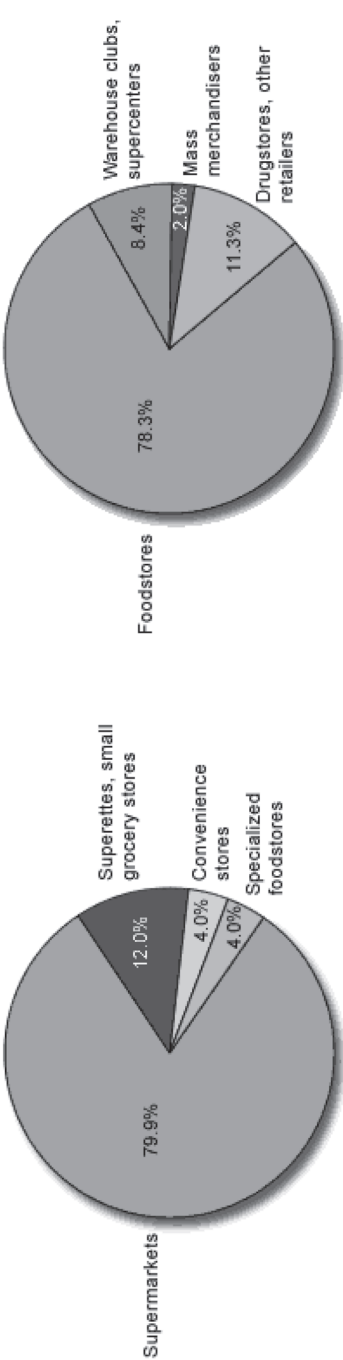


Figure 6.14 Concentration in food processing and retailing.
 (A) Concentration ratios in US food manufacturing. A handful of companies control more than 50% of most agricultural markets in developed countries. (Source: Hendrickson and Heffernan, 2002).
 (B) Global expansion of the five largest transnational food retailers, 1980–2001. Each of the five largest global supermarket chains expanded the number of countries where it operates by at least 270%. (Source: UK Food Group).



Sources: *Estimates of Monthly Retail and Food Services by Kinds of Business, 2002*, Census Bureau; *The U.S Food Marketing System, 2002*, ERS.

Source: *Food Expenditures data series, ERS*. Includes retail store sales only, nonstore sales are excluded.

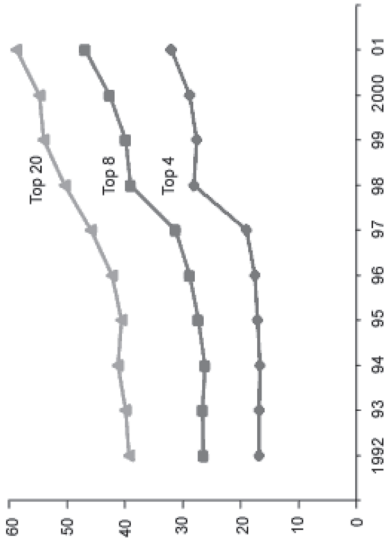
Food sales by segment, 2002

Warehouse club stores and supercenters are the fastest growing segment

Retailers are consolidating

The 20 largest food retailers captured nearly 60 percent of total grocery store sales in 2001

Percent of U.S. grocery store sales



Note: Sales based on North American Industry Classification System (NAICS).
Sources: Monthly Retail Trade Survey, Census Bureau; company annual reports.

Figure 6.15 The US food retail market.
Total food and nonfood sales reached
US\$ 449 billion in 2002.

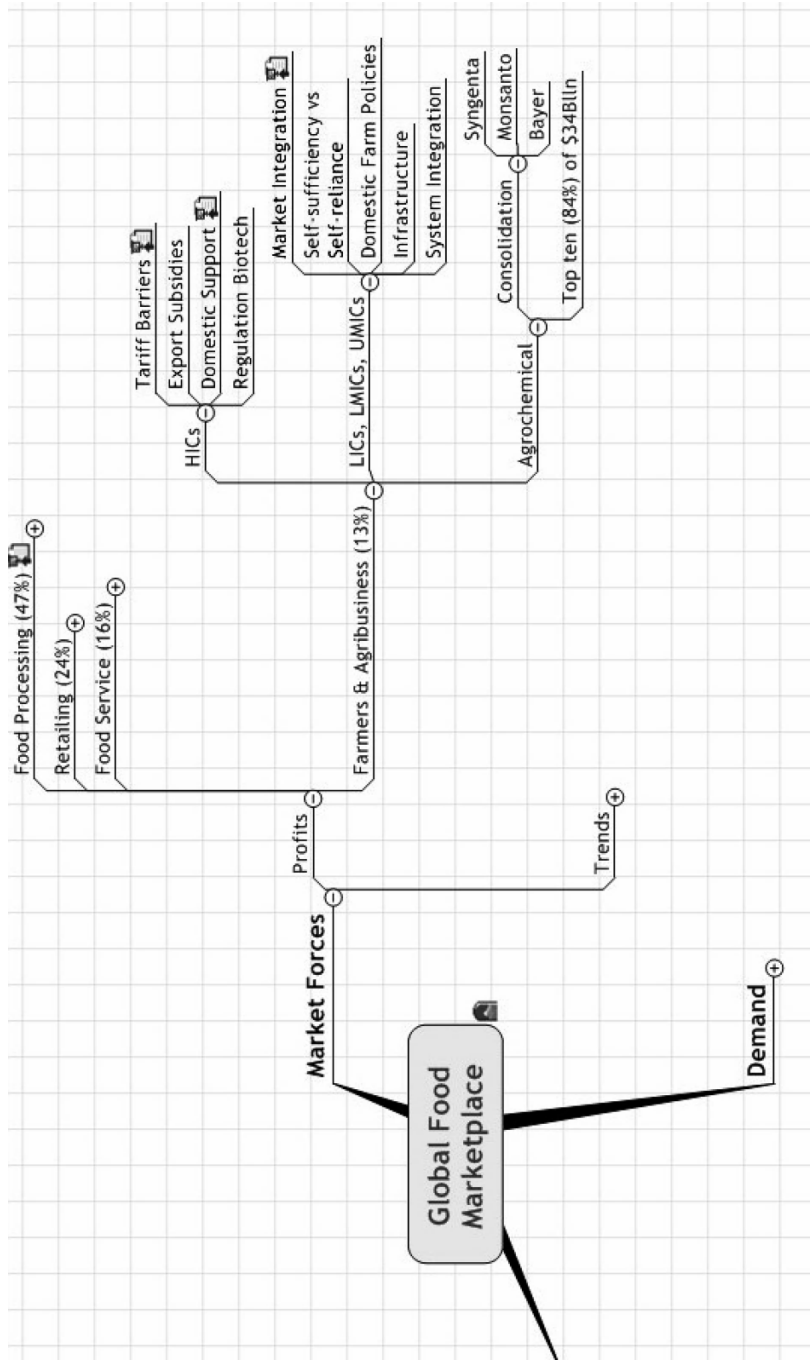


Figure 6.16 The global food marketplace map. (6) Farmers and agribusiness.

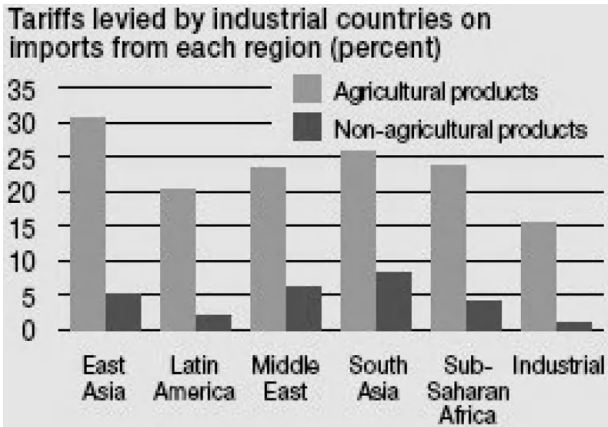


Figure 6.17 Developed countries' tariffs on agricultural and non-agricultural products by region, 1997. Developed countries level much higher tariffs on agricultural products from developing countries than on those from other developed countries. (Source: World Bank).

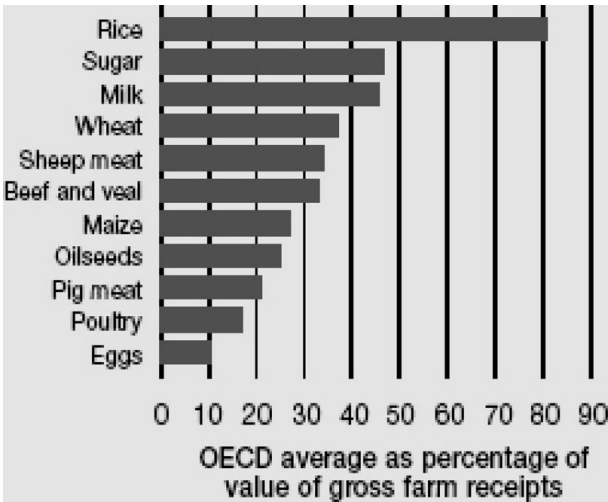


Figure 6.18 Subsidies to agricultural producers in OECD countries. Producer support estimate (average 2000–2002). (Source: OECD).

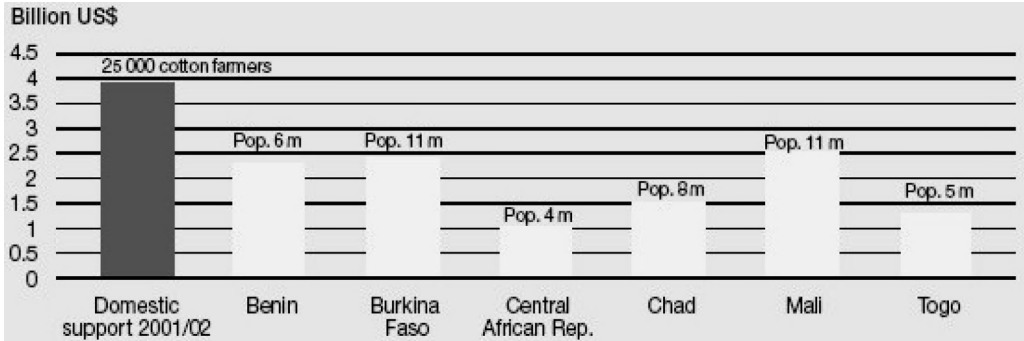


Figure 6.19 US domestic support for cotton and gross national incomes for selected West African cotton growing countries. (Source: FAO).

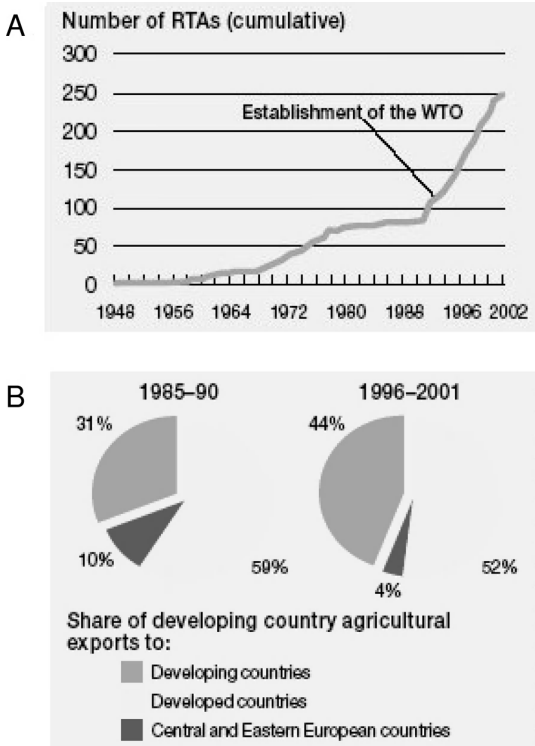


Figure 6.20 Developments in global agricultural trade. (A) Regional trade agreements (RTAs) notified to the GATT organization, 1948–2002. The number of RTAs has grown at a rate of 15 per year since 1995, more than five times the rate during the previous 45 years. (Source: WTO).

(B) Increase in agricultural trade among developing countries since 1985. The share of agricultural exports from developing countries that went to other developing countries increased from 31 to 44% between 1985–1990 and 1996–2001. (Source: FAO).



Figure 6.21 Membership in regional trade agreements (RTAs) and emerging megablocs of RTAs, 2000. (Source: WTO).

6.5

Market Trends

With regard to trends in the marketplace, there has in recent years been a fusion of businesses, of industries, and of the sciences to create the new health and wellness market (Figures 6.22 and 6.23). The risk of disease comprises malnutrition on one hand and obesity on the other hand, in addition to obesity-linked diabetes (referred to as “diabesity”) which is especially prevalent in developed countries, and very specifically in the United States. This trend of wellness, together with the risks of disease and trade organizations, are changing the global food economy. An example of this is the world coffee market, where only four international traders and 25 million farmers and workers are connected via three roasters and 30 grocers to 500 million consumers (Figure 6.24). The share of final sales attributable to the different links in the coffee value chain is especially important for low-income countries (Figure 6.25A). The same situation is encountered with other agricultural products, for example bananas (Figure 6.25B).

6.6

A Self-organizing Market?

The point to be made here is why, and how, does such a consolidatory situation arise whereby a very small number of companies are in control of the entire operation. A 1995 report to the European community included an important

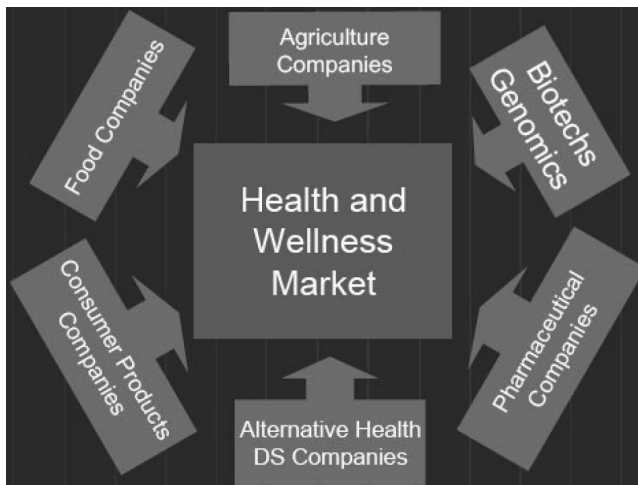


Figure 6.22 The many players in the emerging wellness market. (Source: Burrill and Company).

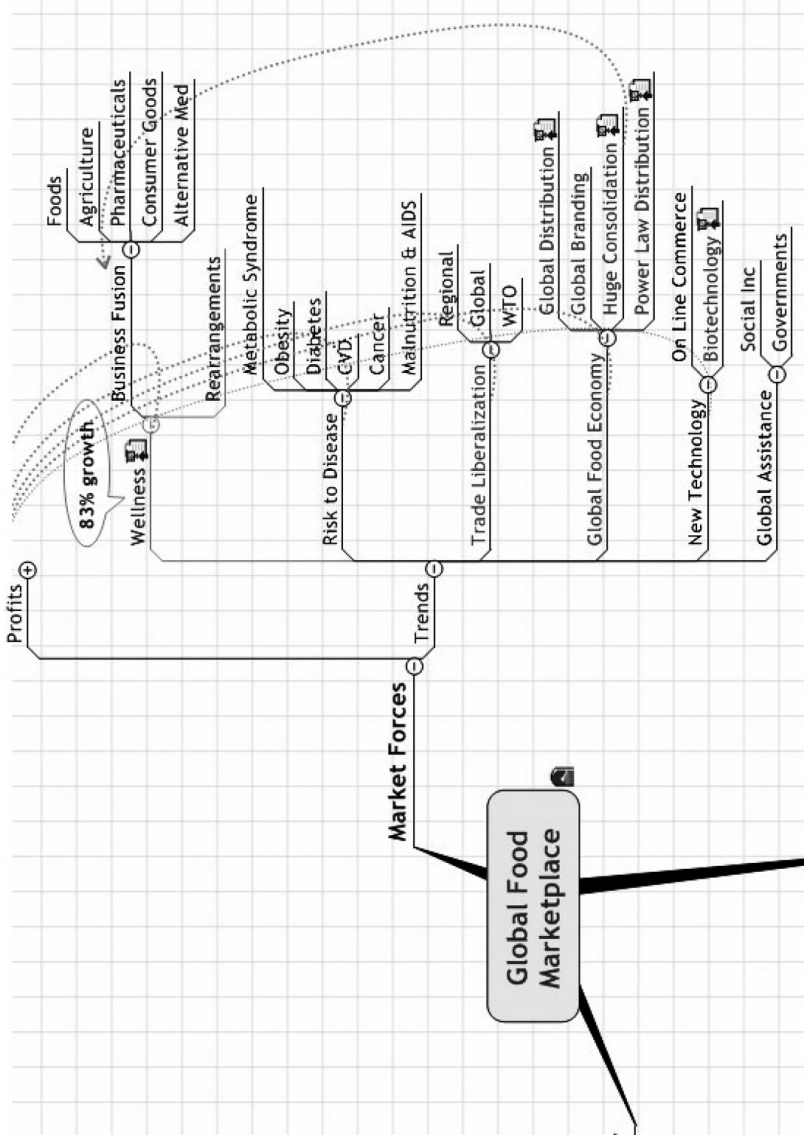


Figure 6.23 The global food marketplace map. (7) Trends.

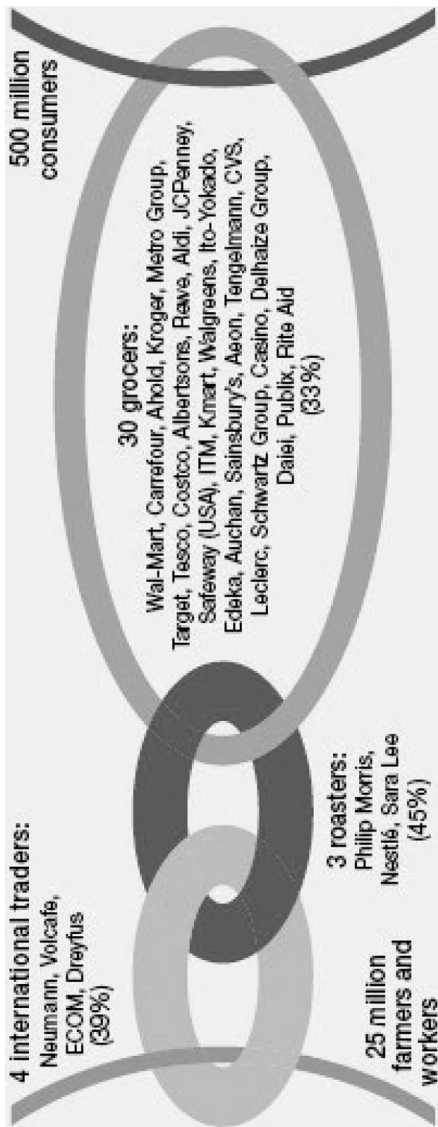


Figure 6.24 Concentration of market power in the global coffee value chain. (Source: UK Food Group).

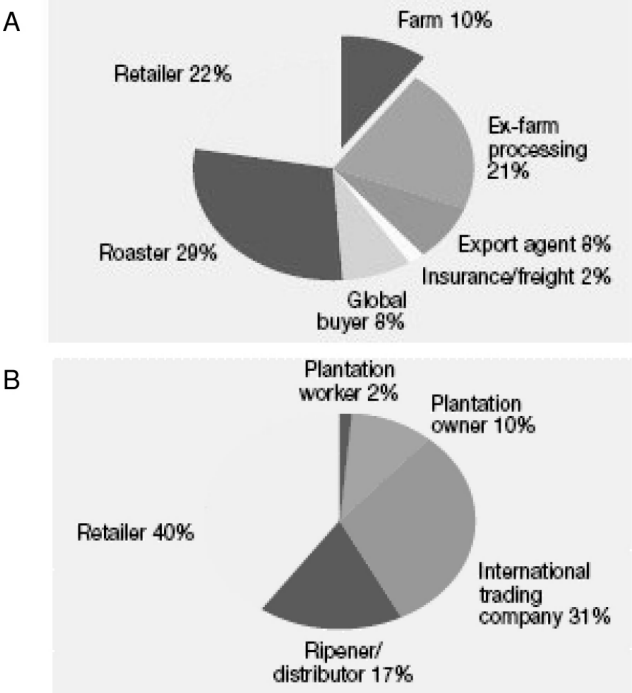


Figure 6.25 Share of final sales value accruing to different links in the value chain for coffee (A) and bananas (B).
(Sources: Africa Beverage Project and UK Food Group).

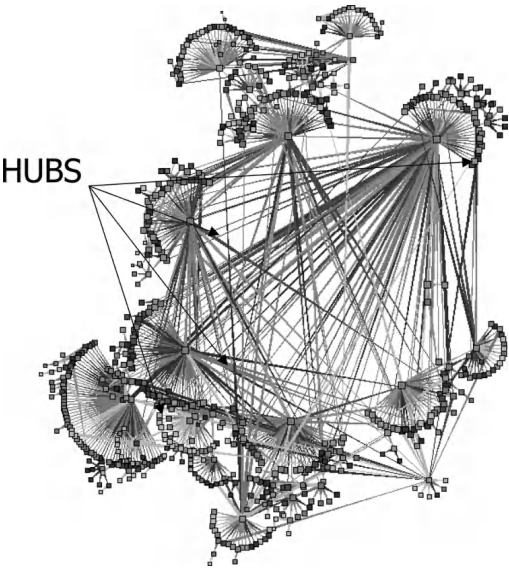


Figure 6.26 Connectivity in the internet.

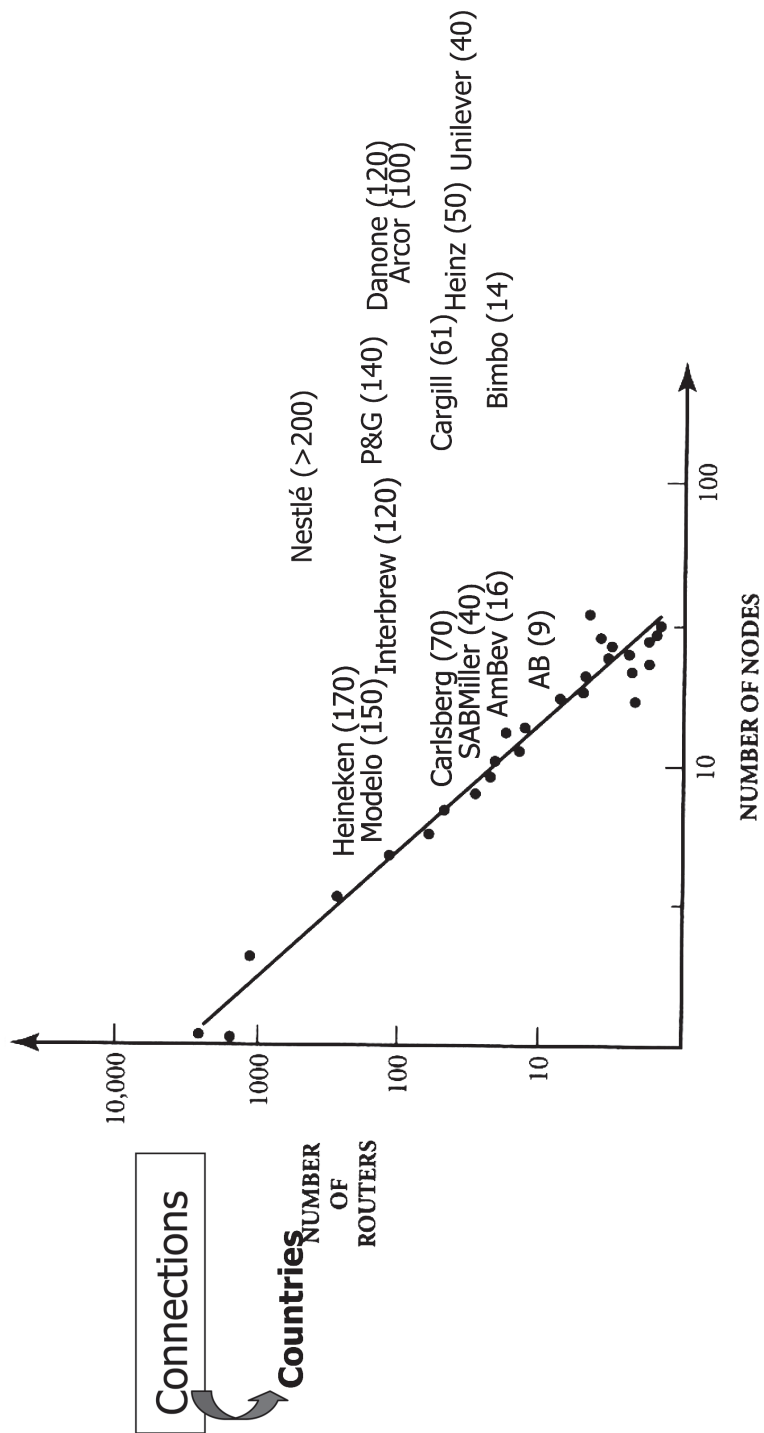


Figure 6.27 Power laws govern the number of connections in the internet (dots) as well as the number of countries in which companies in the food and beer sector are active.

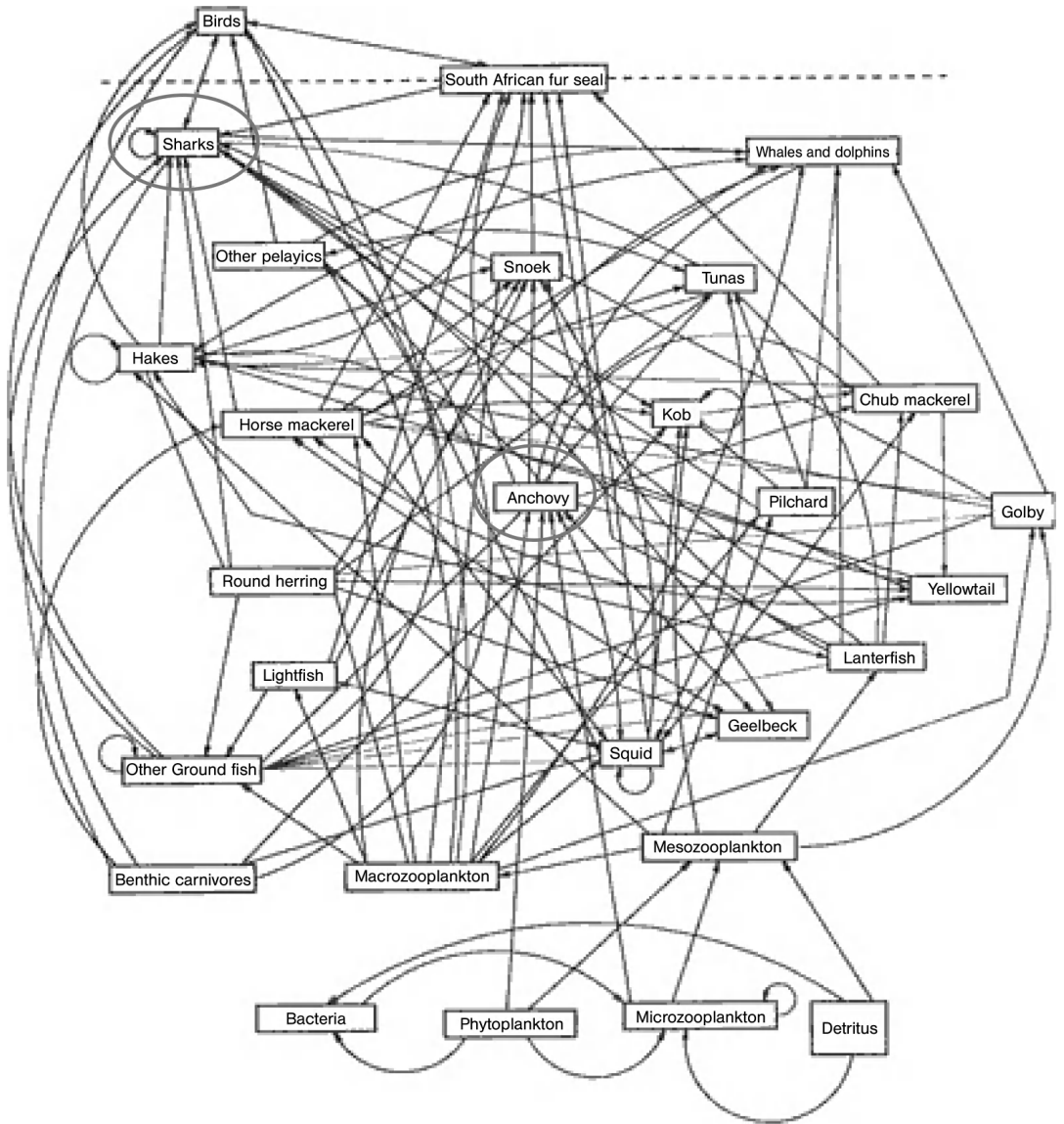


Figure 6.28 The aquatic food web. An arrow from one species to another indicates that the second species consumes the first species. (Source: S. Kauffman, *Investigations*, Oxford University Press, 2000).

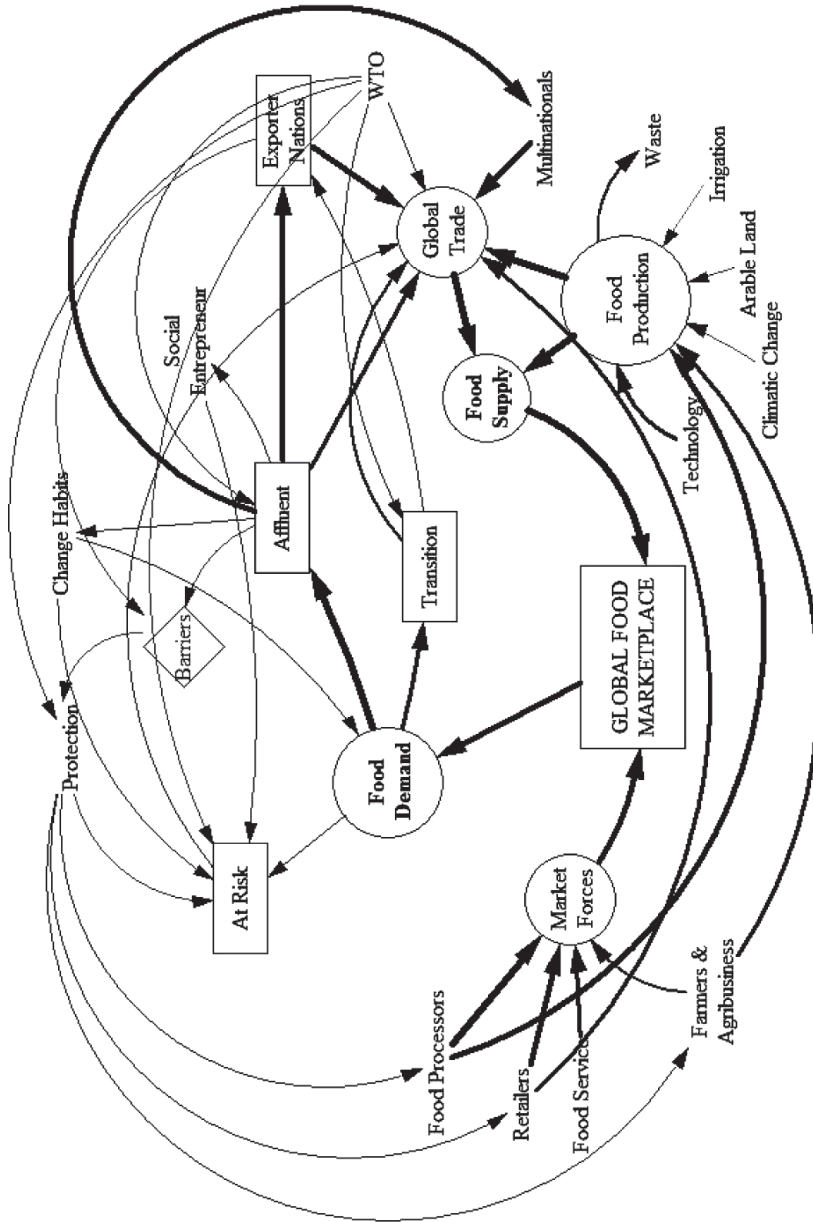


Figure 6.29 The global food marketplace.

statement that: “The maintenance of organization in nature is not and cannot be achieved by central management, order can only be maintained by self-organization”. Subsequently, Albert-László Barabási, a physicist, took this one step further, in stating that “... the road from disorder to order is maintained by the powerful forces of self-organization and is paved by power laws. They are the signatures of self-organization and complex systems”.

Figure 6.26 illustrates diagrammatically the graphic expression of a power law; in this case it is the Internet, where some nodes in the network which have millions of connections, whilst others have only one to three connections. In this way, there is a very small number of highly connected nodes that control the entire network, and if the number of linkages is plotted against the number of nodes, most nodes have very few connections, whilst very few nodes basically have all the connections (Figure 6.27). This is exactly the situation that occurs with social networks.

If this principle is applied to food and beer, for example, the connections all follow the power law, the interesting point being that this power law applies to all types of networks. The same topology is identified within the Internet, within the telecom business, in an intranet; it occurs in an e-mail network and, within a biological context, among neurons. In other words this is a universal phenomenon, and it explains why a very small number of grocers control everything in the food marketplace, why very few laboratories are the leaders in vaccine production, or very few institutes of agricultural research are responsible for all the technological progress that has been made.

An excellent example of a typical “marketplace” is that of the aquatic food web (Figure 6.28), where there is one very powerful node of the sharks, and a secondary hub of the anchovies. In this case, the latter are eaten by all of the others, whilst the former eats most of the others.

A similar situation seems to occur in the global food marketplace, where there is a food demand and a food supply (Figure 6.29). Here, the demand is dominated by a very few nodes, and hence this area would be very weak. Complexity is managed by self-organization, which expresses itself by power laws, namely by scale-free networks, such that the entire system would collapse if the weaker areas of the networks were not attended to. There are forces already at work that will fix the marketplace, the major force being global trade. But, trade must be fair – in other words, the existing trade barriers will have to be lowered.

Of course it will also be necessary to attend to the people at risk. For example, there may be so-called social entrepreneurs from affluent countries which dominate everything, and no doubt will continue to dominate. However, because of these self-organizing forces the links in the network that are currently very weak will become stronger. Hopefully, this chapter has highlighted some of the forces that dominate and shape the global food marketplace.

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Module III

Feeding 9 Billion People by 2050

Introduction

Dominique Lecourt

Demographic projections suggest that the world population will reach 9 billion by 2050, and that the vast majority of these people will continue to live in rural zones. Whereas we are unable to nourish the 6,4 billion inhabitants of our planet today, how can we provide for a greater multitude tomorrow? This is a frightening challenge for scientists, industrialists and, obviously, the entire society. How can we encourage greatly increased investment in public research in this sector? How do we convince the private sector to engage in more enlightened self-interest by not limiting its financing to the rich countries of North? Could this challenge be taken up in the absence of international regulation regarding GMOs, if such regulation is unfavourable to the countries of the South? It is impossible to avoid the question of agricultural and trade subsidies which operate to the serious disadvantage of developing countries. Now is the time to inform and train these farmers. How can women be educated on a massive scale which would enable them to understand the advantages of biotechnologies, and the time and work that they could save? Couldn't such an action include the NGOs concerned with the environment and sustainable development?

Author Biography

Peter Raven



Director, Missouri Botanical Garden

Peter H. Raven has served as Director of the Missouri Botanical Garden and Engelmann Professor of Botany at Washington University in St. Louis since 1971. A student of plant systematics, evolution, and biogeography, he has become a global spokesperson for the conservation of biodiversity, while the Missouri Botanical Garden has become one of the world's leading institutions engaged in the study of plants and promoting sustainability around the world. A graduate of the University of California, Berkeley, he earned his Ph.D. degree from the University of California, Los Angeles, and taught at Stanford University before moving to St. Louis. Peter Raven is the author or editor of about 20 books, including *The Biology of Plants*, now in its seventh edition, and several hundred scientific papers. He served as home secretary of the U.S. National Academy of Sciences for 12 years, and is a member or foreign member of a number of other academies, including the Royal Society, the Pontifical Academy of Sciences, the Third World Academy of Sciences, and the national academies of China, India, Russia, Mexico, Brazil, Chile, Australia, Argentina, Sweden, and Denmark, among others. He is a recipient of the U.S. National Medal of Science, the International Cosmos Prize (Osaka), Sasakawa Environment Prize, Tyler Prize, and Volvo Environment Prize, and other awards, and has served as president of several scientific organizations, including the American Association for the Advancement of Science. Peter Raven was president of the XVI International Botanical Congress in St. Louis in 1999. He has been recognized by TIME magazine as a "hero for the planet", on the basis of his conservation activities. Currently he chairs the Division of Earth and Life Studies in the U.S. National Research Council and the Committee for Research and Exploration of the National Geographic Society, and is Vice President (former President) of Sigma Xi, the scientific honor society.

7

Feeding the Nine Billion: The Challenge to Science

Peter Raven

7.1

Introduction

It is estimated that the world population may stabilize at about nine billion people at the middle of the 21st century. However, whether it stabilizes or not depends on mankind's continued involvement with and devotion to family planning around the world, to increasing opportunities for women, and to continuing to regard this as an important goal to which a great deal of attention must be paid. If attention is not paid, then the population certainly will not stabilize automatically. Although global population in percentage growth peaked in 1971, and in numerical growth in 1992, there is no assurance that this trend will continue unless interest is sustained in this topic.

One of the most important points to remember about agriculture is that the development of crop agriculture, in today's sense, began not much more than 10 500 years ago at the eastern end of the Mediterranean. That is about 425 human generations ago, and it is at the end of two million years of human existence on Earth. This in fact is a very short space of time. It is not to say that the approximately three million people who lived on Earth at that time agriculture was developed, and their ancestors over the preceding two million years, did not have a major environmental effect on the Earth. Indeed, for many years previously they had learned to build and nurture fires, and to burn off grazing lands and kill large animals that were ecosystem-dominant. But, with the invention of crop agriculture and the domestication of animals which soon followed, the population numbers began to swell, and man's activities became much more widespread.

It has been estimated that, by the time of Christ, the world's population had grown to about that of Europe at present – some 300 to 350 million people. It must be remembered, however, that this population was spread throughout Eurasia, Africa, North and South America and Australia. Consequently, it

had a much lighter impact on the environment than has been experienced in recent decades.

7.2

World Population Growth

During the 1790s, Thomas Malthus predicted that population growth might outstrip man's ability to produce food, and widespread starvation might ensue. At that time, the population of the entire world was about 900 million people – considerably less than the present population of either China or India. Malthus' predictions proved not to be true because of the onset of the industrial revolution, which had actually begun a few decades earlier in Great Britain and was in the process of spreading throughout the world. This revolution made possible much more efficient ways of cultivating soil and ways of synthesizing fertilizers and applying chemicals. Likewise, the development of the steam engine and other powered machinery made agriculture more efficient from the 1790s onward. It is clear that many hundreds of millions of people have died of starvation from 1790 to the present day, and so Malthus was not entirely wrong. The global population crossed the billion barrier early in the 19th century, but took another 120 years to reach two billion, in about 1930. The total then progressed to 2.5 billion people in 1950, and between 1950 and 2000 grew from 2.5 billion to 6.3 billion (Figure 7.1). This was an unprecedented expansion of what was already the largest population that the world had ever known, by far. Where population numbers go in the future has already been discussed.

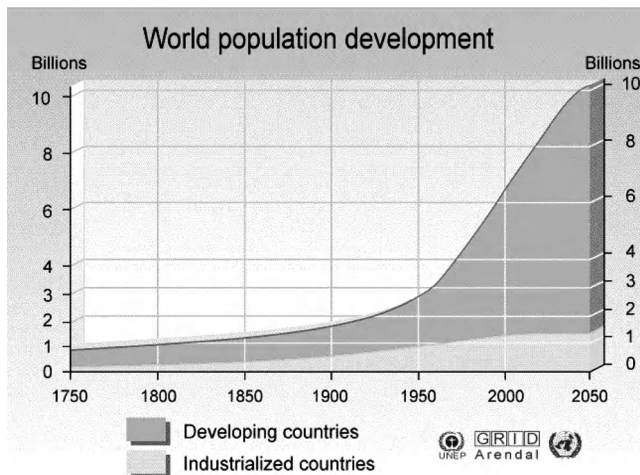


Figure 7.1 World population development, 1750 to 2050 (estimated).

Among the current 6.3 billion people inhabiting the world, half have a daily income of less than US\$ 2, and one in eight people is literally starving in terms of caloric intake, receiving less than 90% of the UN recommended minimum 2000 calories per day. In addition, one in two people, according to the World Health Organization, is malnourished in terms of some essential nutrient. This is not the world often thought about by those living in an industrialized country, where it is all too easy to feel that everything is all right. And that, cast in the glow of the report of the world commission on environment and development of the late 1980s, all countries will soon come to enjoy the standards of living enjoyed by industrialized countries. It is also very easy, while living in a developed country, to think of population as the only driving force behind world destabilization. It is very important to remember that it is the products of population and of affluence or consumption levels, and the uses of technologies that create pressures on the Earth. Put another way, a citizen in an affluent part of Europe or the US lives at about 40 times the rate of consumption than does a citizen of rural Brazil or rural Indonesia. For example, when it comes to potentially sustainable environmental resources, the impact of the 140 million US citizens that have been added since the end of World War II is approximately equal to the entire impact of all people living in developing countries in the entire world. One of



Figure 7.2 Urban areas and land use in different parts of the world.

(A) Urban sprawl in Mexico City; (B) Ranchettes in Colorado (USA);
(C) Smog over Los Angeles; (D) Golf course on potential fertile farmland.

the world's larger cities – Mexico City – has been developed in an ancient lake bed (Figure 7.2A), whilst in the affluent United States the countryside is being cut up everywhere into small ranchettes, which consumes the land but leaves none of it in a natural state (Figure 7.2B). The result is that everybody has about 1.5 hectares with weeds growing on it, somewhere in the country and usually 20 to 40 miles from their workplace, to where they drive every day using artificially subsidized gasoline in large, high-petroleum-burning cars. In Los Angeles (Figure 7.2C), photochemical smog is the rule of the day. The American comedian, Jack Benny, once said, "Ah, Los Angeles, where you wake up to the coughing of the birds".

7.3

Cultivation Areas

Estimates made during the run-up to the 1992 Earth Summit in Rio de Janeiro indicated that, since 1950, about 20% of the world's topsoil had been lost, and almost 20% of the world's agricultural land had been lost to urban expansion, salinization, desertification and other features as the population expanded from 2.5 to 6.3 billion. About one-third of the world's forests of 1950 were lost during the ensuing 50 years, without being replanted. Levels of carbon dioxide, the major gas produced by human that induces global warming, were increased by about one-sixth during the same 50-year period, and continue to grow alarmingly. Today, there is about a 6–8% loss in the stratospheric ozone layer, which means that the incidence of malignant skin cancer in Europe has risen by 20% from 1950 levels, due to ultraviolet B radiation penetrating the atmosphere in greater amounts. Spreading deserts everywhere have threatened agriculture and human existence, and all too often, with the world becoming increasingly populated, a situation has occurred where populations have expanded during periods of unusual drought.

Of the world's land surfaces, approximately 11% is devoted to crop agriculture today. This is about 80% of the area cultivated in 1950, with few exceptions such as the Sahado of Brazil where soybean cultivation is now spreading through every last square centimeter, and a few nature reserves. Today, it appears that all land in the world that can be cultivated is being cultivated. There are no great reservoirs of uncultivated land ready to be brought into cultivation to save mankind. A considerable amount of arable land is being lost every year to salinization, desertification and, because of urban sprawl, very large areas of the Earth's surface are being converted to cities. For example, the municipalities of cities in China own the land around them, and are rapidly selling adjacent farm land for development. Unfortunately, this is happening worldwide; for example, the central valley of California is being converted to one megalopolis as the Californian population rockets

towards an anticipated 60 million. Within 20 years, there will be more people living in California than in Great Britain.

Perhaps more significantly, over 20% of the Earth's land surface is being used for natural pastures, most of them unsustainable. In fact, there is scarcely any place in the world where animals persistently graze natural vegetation that is sustainable. China found out, much to its dismay, that over the past 10 to 15 years it had expanded northward into natural grasslands, only to find that these lands were soon reduced to desert under the impact of grazing. The country is now engaged in trying to retool those pastures into alfalfa and other crops that can be grazed on a sustainable basis. About 11% of the world's soils can be farmed without being irrigated, drained or otherwise improved, although farming such land becomes more difficult and more expensive on the margins (Figure 7.3). The main lesson is that the land being cultivated now must be handled well, not only from the point of view of productivity but also sustainability. Summarizing this information in a different way, mankind is either directly wasting or diverting (diverting would be as in the case of this golf course; see Figure 7.2D) an estimated half of the net terrestrial photosynthetic productivity on land.

Man, as one of about 10 million species inhabiting the Earth, has a current population of 6.3 billion and uses about half of the total photosynthetic productivity worldwide. One-half of mankind lives in absolute poverty, and one-eighth is starving, yet another three billion people are scheduled to be added over the next 50 years. The question, therefore, is how these resources can be marshaled to improve the condition of those who are alive now, much less to bring on board the additional three billion future inhabitants in some

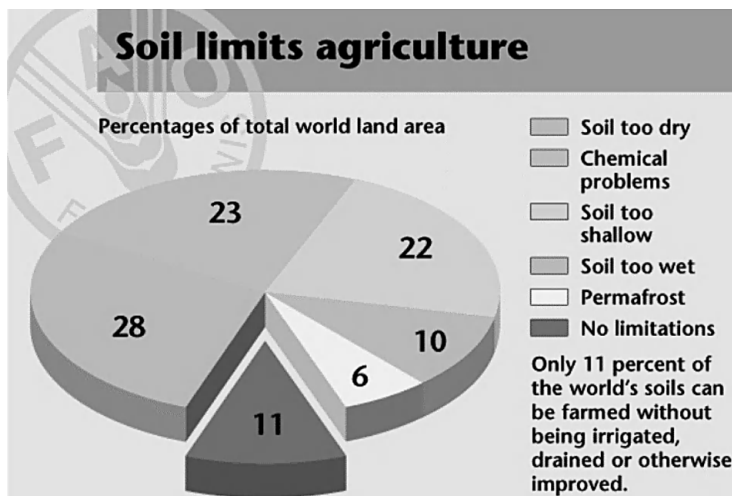


Figure 7.3 Suitability of world soil for agricultural use. (Source: FAO).

kind of humane and socially just way. It is also estimated that, today, mankind uses about 55% of the sustainable supplies of fresh water in the world. With a billion or more people having no access to any kind of reasonable supply of fresh water, and again three billion people to be added, the water table in the North China plain (which produces about 40% of China's food) is falling by about 1.5 m per year. Likewise, the water table in most parts of India, the population of which rises by one million every 12 days, is falling by about 1 m per year. In fact, salt water is encroaching all around the shoreline of India, and this is wrecking the rice crop in many areas that were formerly fertile. Similarly, it seems likely that Saudi Arabia, which relies on artesian water for agricultural purposes, will be unable to continue their net export of wheat.

7.4

Biodiversity and Poverty

The relationship between biodiversity and poverty is very important because biodiversity symbolizes sustainability. The estimated 10 million species of eukaryotic organisms in the world (bacteria excluded, as there is no reasonable way to estimate their numbers) include about 300 000 types of plants, of which about 100 provide 90% of the calories ingested by man, either directly or indirectly. Three types of grass – rice, maize and wheat – provide about 60% of all calories consumed directly or indirectly. The biodiversity of individual crops, as suggested by cobs of maize grown near Puebla in Mexico (Figure 7.4),



Figure 7.4 Biodiversity in food crops, as exemplified by a selection of maize cobs from Puebla (Mexico).

close to where maize was developed, indicates the need to save crop diversity much more efficiently than has been done in the past. This should allow the staving off of emergent diseases that will continually – and increasingly – threaten the increasingly homogeneous crops grown worldwide. Thus the biodiversity of plants, and of organisms in general, is of great importance.

An additional point that must be borne in mind, particularly for those living in the industrialized world, is that for two-thirds of the world's population plants serve as medicines. The great traditions of India and China provide medicine for a large proportion of the population, and are therefore of great importance. But these are also in great danger, as the traditional medicines are being harvested and shipped to First World countries. In fact, this has occurred to the point where many traditional species are now endangered.

It must be remembered that at least 25% of prescription drugs worldwide are either based on natural products developed from plants, or are extracted directly from plants, microorganisms, fungi or animals. With between 4000 and 5000 types of antibiotics having been prepared from fungi and bacteria since the end of World War II, the opportunity for many more such discoveries is clearly enormous. It must also be remembered that it is only just over 50 years since the first ideas were conceived of the double helical structure of DNA, by Watson and Crick. That represents a very short time span, and it is likely that more groundbreaking discoveries such as the recent announcement (Lolle et al., *Nature* 434, 505–509, 2005) of silent genes reposing in plants, which were earlier non-mutated versions of the mutations elucidated in *Arabidopsis* and which might replace genes in mutant varieties being studied, lie ahead. This is simply the tip of the biotechnology iceberg, and it is clear that many similar discoveries are still likely to be made in the field of molecular biology. It is only 32 years since Boyer and Cohen first transferred a gene between unrelated species. The use of genetically modified plants is in its early stages, with to date, only 10% of the world's cropland and eight 8 million farmers – seven million of whom farm in developing countries – utilizing this technology. However, it stands to reason that there is a very long way to go. Mankind is at the doorway to an age of genomics.

7.5

Genetic Engineering

The genetic engineering of papayas to create virus-resistant crops that would save the papaya growers of Hawaii is just one example of many that will continue to emerge worldwide as agriculture becomes more precise, sustainable, and productive (Figure 7.5). The battles being waged today over GMOs are clearly transitory – though very staunch – as no evidence has been provided that the transfer of a gene from one species to another causes any intrinsic danger.



Figure 7.5 Field trials of transgenic ringspot-virus resistant papayas in Hawaii. “UH rainbow” transgenic papayas are unaffected by the virus, as seen by the dense growth in the center (top) and on the right-hand side (bottom) of the field, while the nontransgenic “UH sunup” plants have suffered greatly.

Rather, it is the products that must be examined, but as hundreds of millions of people worldwide have eaten genetically modified foods continuously without a single case of illness resulting from any such food, this subject becomes somewhat tedious. Currently, trials are being conducted in the UK and elsewhere with GMOs, and the pure crops that have always been desired in agriculture have been attained, with less room for biodiversity but more room for crop productivity. In future, these fields might be prepared in any form, and engineered – that is, planted and prepared – for any particular situation.

7.6

Global Warming

Global warming represents a major threat to future agriculture, and is a source of national embarrassment in the US and, presumably, also in Australia – who have neither ratified the Kyoto protocol nor taken adequate steps to begin addressing the problem of anthropogenic greenhouse gases. In Russia, people fantasize that global warming will benefit them by allowing crops to be grown more widely. However, if the world's population is to rise from 6.3 to 9.1 billion, then simply moving agriculture around is a no-go situation. It is impossible to move huge cultivated areas with good soils to other areas with poor soils, or perhaps to move cities in order to free the land for agriculture. For example, if the hurricanes that devastated Florida in 2004 had occurred 125 years ago, they would not have been reported in the news because there were no people living there. Put another way, if Krakatau – which erupted in the 1880s and killed an estimated 30 000 people with a tsunami 50 meters high – had occurred in 2005, instead of the tsunami with a wall of water 10 meters high which killed 300 000 people, it is easy to imagine what the consequences might have been. Industrialized nations tend, to some extent,

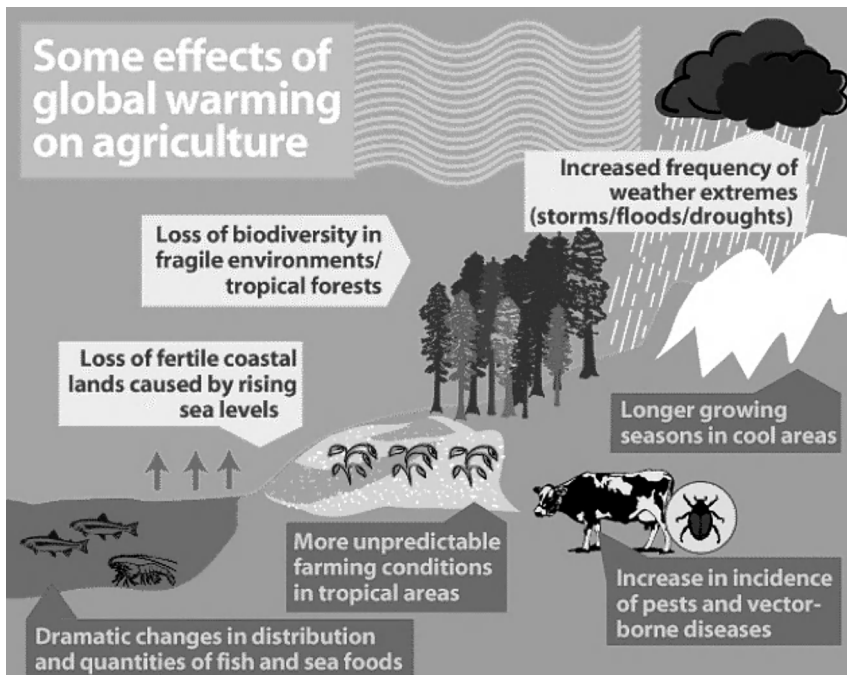


Figure 7.6 Effects of global warming on agriculture.

to pretend that global warming is not a problem for them. In fact, it is a huge problem for everyone, and something that must be acknowledged not only at a Kyoto level but also at a much more profound level if agriculture and productivity are to be sustained in the future (Figure 7.6).

7.7
How Many Planets?

One important way to view all of this is to ask this question taken from the so-called “Brundtland Report”: Can all nations achieve the standards of prosperity enjoyed now in the industrialized countries if the available technologies continue to be used? This report of the world commission on environment and sustainability in 1986 introduced wide use of the term “sustainability”, and presented a scenario in which poor developing countries can advance to the standard of industrialized countries if simply given the chance. How this can be done is not clear, however. Wackernagel and colleagues, at a “think tank” in Oakland, California, calculated how many planets would be needed under various circumstances by using a variety of explicitly detailed parameters (Figure 7.7). This group has estimated that, to support everybody at current population levels and living standards – that is, without improving anybody’s lot on earth – it would take about 120% of the annual productivity of the world.

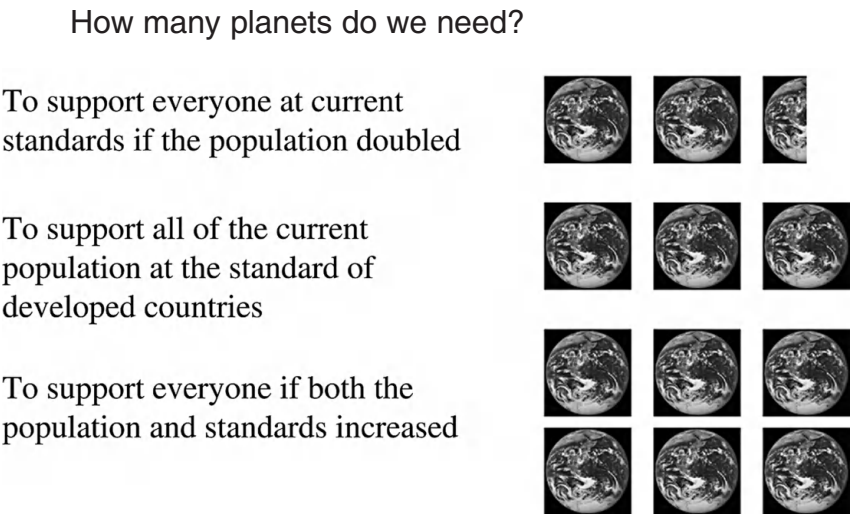


Figure 7.7 Estimated annual productivity of the world at current levels in comparison with future needs. The data underlying the figure are based on a study by Wackernagel and colleagues.
(Source: M. Wackernagel et al., Proc. Natl. Acad. Sci. USA 99, 9266–9271, 2002).

That is opposed to an estimated value of 70% as recently as 1970. What this means is that the world is being degraded progressively and very rapidly using current technologies and current levels of consumption, without making any improvements at all. So how many planets would be needed if the current population were to be doubled? Clearly, the number would be 2.4 if no changes were to be made in terms of current patterns of consumption or technology.

Those planets are clearly not available. Moreover, if the suggestions of the Brundtland Report were to take place without any improvement either in the ways in which items are consumed or in the technologies used to obtain them, then three planets would be needed to support the current population at the level of industrialized countries. This is a very important consideration, especially as automobile use and highways and railroads spread throughout China. The question is, where is this all going, and why are we simply replicating inappropriate technology worldwide when there is no future to it? In the 1960s, a calculation was made of the cost to export people to the nearest star likely to have planets (like Earth). The suggested result was that if the entire world gross economic product were to be used, only 12 people could be exported each year. Clearly, if both the population and standards increase, then there is an impossible scenario, and this is a clear signal that we must reach a sustainable world. This is not a matter of choice, it is not a matter of social justice alone, it is not a matter of morality, and it is not a matter of creating a sustainable world so that industrialized countries can benefit from it. We must reach both a sustainable population level and sustainable levels of affluence or consumption, and technologies must be found to replace those presently in use, or it will not be possible to manage the world in a sustainable fashion.

7.8

The Way Forward

In order to move forward, we must attain global sustainability as a condition for human progress, and address the issues referred to here. Within that formula, however, agriculture is the key component that would affect man being able to achieve sustainability. It will also depend on the sustainment of sustainability. The question to be faced then is whether all of the forests will be cut down and made into unsustainable fields using current levels of technology, or whether agriculture will be concentrated and intensified in the correct places to be able to support mankind, while still leaving natural areas. A globally sustainable world is a necessary condition, but this can only be achieved in a socially just world, and the way in which agriculture is managed is a major factor in making that possible. There is a need, for example, to reduce emissions that both poison people and change the character of the world's climate. Today, 82% of the global population lives in developing



Figure 7.8 Philippine girls gathering water from the mercury-containing effluent from a gold mine.

countries but controls less than 20% of the global economy; this sector of the population includes only 10% of the world's scientists, who are largely concentrated in China, India, Brazil and Mexico. Another 40% of the world's population live in about 150 countries which are mostly very poor and have very little scientific or technical capability that would enable them to better their lots. In the Philippines, for example, an estimated 70 to 80% of the people live in absolute poverty; the water the two girls on the picture bring home is an effluent from a gold mine where mercury is used to separate the gold from the ore. It is not difficult to imagine the consequences (Figure 7.8)!

We must become used to thinking about such scenes from a moral and a sustainable perspective if countries around the world are to be helped. Figure 7.9 illustrates GDP growth worldwide, and provides an idea of the mal-distribution that occurs. Future agriculture, in order to achieve what is needed, will need to utilize many approaches simultaneously (Figure 7.10). Genetic technology, although sometimes characterized as a "magic bullet", is not a magic bullet – it is simply one of many systems required to produce the sustainable and productive agriculture of the future. It is part of what is needed to conserve genetic diversity. Extension is required through the poor farmers of the world. I know of no farmers living in rural areas anywhere in the world who are better off today than they were 20 years ago. The lack of information, the concentration of information and opportunities in cities, the fluctuation of agricultural prices in a global economy, are all threatening agricultural welfare around the world.

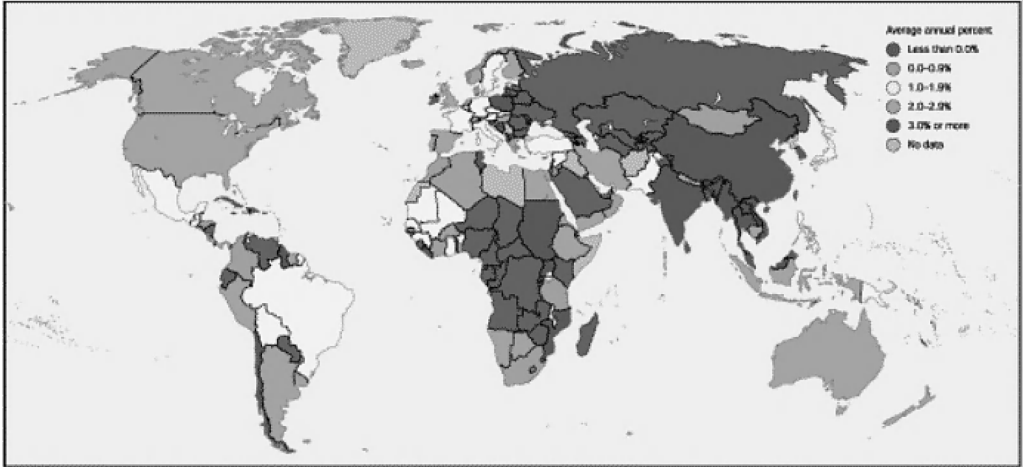
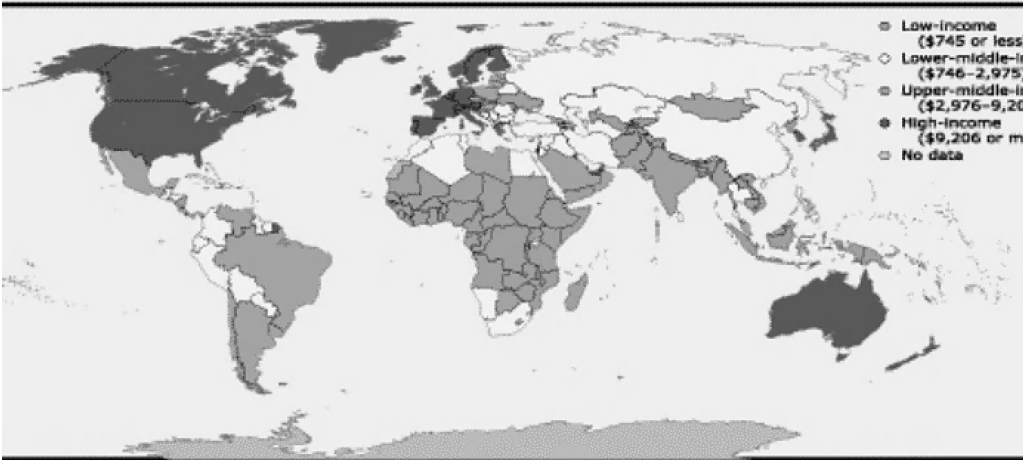
GDP per capita growth, 1990-2001**per capita, 2001**

Figure 7.9 Gross domestic product (GDP) growth during the last decade of the 20th century (top) and GDP per capita values in 2001 (bottom).

- Integrated pest management
- Reduction of chemical use
- Water conservation
- Genetic modification by traditional and contemporary methods
- No-till practices
- Precision agriculture
- Conserving genetic diversity
- Specialized crops

Figure 7.10 Requirements and responsibilities in the future development of agriculture.

Women are particularly disadvantaged, as around the world women and children in many poor regions are so burdened with gathering firewood and water that they have no opportunity to receive any education. Moreover, they have no opportunity to contribute what they otherwise could contribute to the development of our common future. This is not only immoral and unacceptable – it is extremely unwise because it means that a very large proportion of the brains in the world are simply not being utilized for a common effort in the way that they should. One of the major problems for the future will be to satisfy the food needs of urban populations, but this has not been addressed. Worldwide, 26 cities are expected to have populations exceeding 10 million people within 10 years – at which time at least 6000 tons of food will need to be imported daily into all of these cities (Figure 7.11). It is vital that a great deal more thought is given into how this might be achieved. Growing food locally is clearly part of the solution, but the answer to the problem really lies in people around the world recognizing the situation and working together to improve the conditions for agriculture. In this way it should be possible to conserve the genetic diversity that underlies agriculture worldwide in order to feed the people of the world, to provide adequate technologies that will take care of their needs, and to make those technologies widely available to those people who need them. This is a daunting task, but there is no other way in which a generally prosperous and sustainable world can be obtained. Hopefully, my suggestions might help to kick-start discussions of the steps required to achieve this.

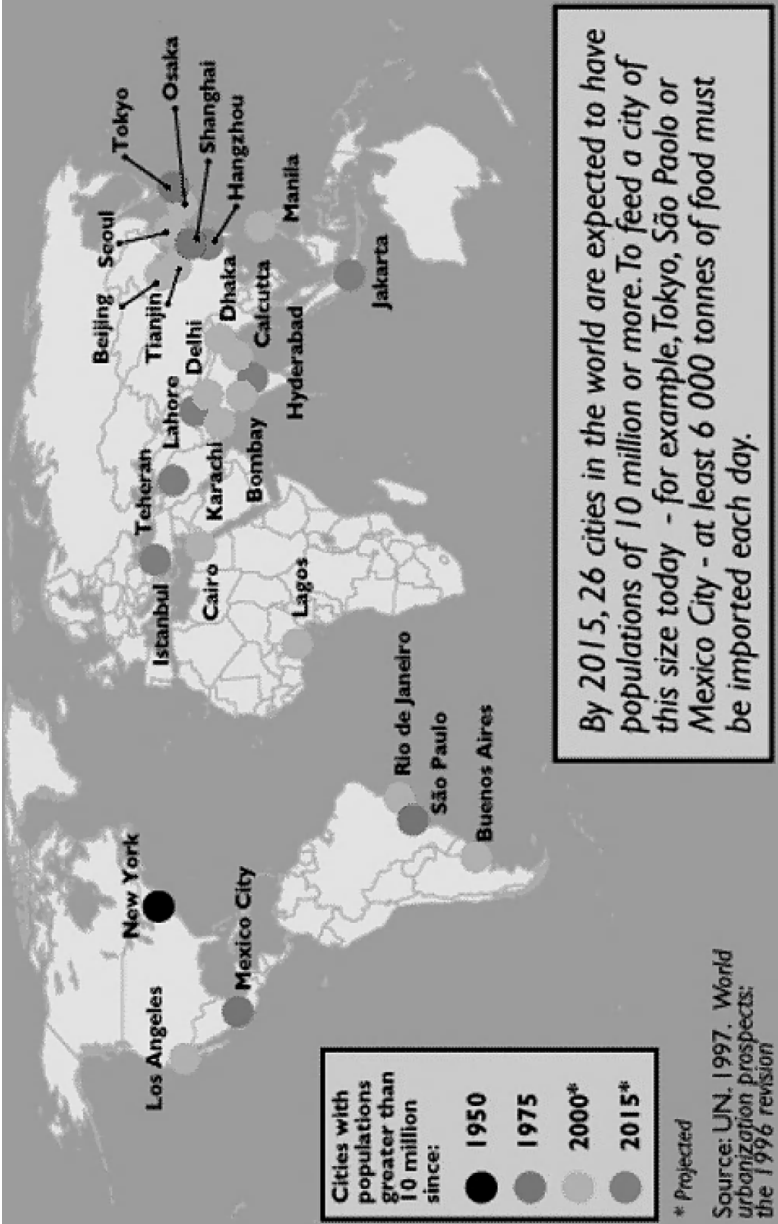


Figure 7.11 Emergence of mega-cities with a population of 10 million inhabitants or more. (Source: United Nations, 1996).

Author Biography

Florence Wambugu



Chief Executive Officer, Africa Harvest Biotech Foundation International (AHBFI)

Dr. Florence Wambugu holds several awards and honors from local and international institutions in recognition of her outstanding work in Africa including first place medal winner in World Bank Global Development Network Awards under science and technology category in Year 2000 for the tissue culture (TC) banana project impact to poor communities. In 2004, she received two awards, which included The Eve Woman of the year Award by the EVE Magazine in East Africa in recognition of her contribution to science/technological application to combat hunger and poverty in Africa; and The South African government commemoration of 10 years of democratic rule for her consistent support to agricultural development. In 2002 and 2005, she was awarded “Woman of the Year” recognition by the American Biographical Institute for empowering contributions leading to increased food production in Africa.

Membership to Professional Boards: Executive Committee member of Forum for Agricultural Research in Africa (FARA), previously 2001–2004 member of DuPont Biotech Advisory Panel-USA, Board of Trustees International Plant Genetics Resource Institute (IPGRI). A member of United Nations Millennium Development goals Hunger Task Force. She is also in the Science Board in Global Health Challenge Bill and Melinda Gates Foundation and Council member of Science Technology and society in Japan under JETRO.

Contribution to Society good through Research and Development: Over the last ten years, Florence Wambugu has successfully provided leadership in public/private partnership and scientific consortium for implementation of various major projects for crops and tree improvement, with significant impact on the livelihoods of smallholder farmers in rural communities. The Tissue Culture (TC) banana project in Kenya and Eastern Africa facilitated under her

leadership has impacted scale farmers from poverty to sustainable livelihoods and is expanding. The project has also been adopted by NEPAD-CAADP and FARA DONATA programs for scaling model project for food security and economic empowerment in Africa. The tree biotechnology project and its private sector offshoots nurseries facilitated by Florence Wambugu who also provided leadership on technology transfer application through public private partnerships is currently supplying over 5 million seedlings of improved tree seedlings a year to rural communities for domestic needs and reforestation. The project is now adopted by Eastern African countries and private sector investors are focused on expanding the impact. Pyrethrum is mainly produced by small-scale farmers in Kenyan highlands. She is credited with conducting the original research work and facilitating the formation of public/private partnership, which led to successful commercialization of the TC pyrethrum production in Kenya; Kenya dominates the global pyrethrum market with 80% market share. Maize streak virus (MSV) is a disease documented to cause over 20% maize yield losses in Sub-Saharan Africa. Florence Wambugu provided leadership to a scientific consortium of local and international institutions to work on different aspects of the MSV disease control leading to development of first MSV resistant maize hybrids in Kenya.

The Genetically Modified (GM) sweet potato project of KARI/USAID Monsanto that she was principle investigator has currently helped Kenya to develop a National Biosafety Regulations opened doors for introduction of other needed GM – crops, and lead to infrastructural development of has a biotransformation laboratory giving Kenya a lead in Eastern African region in relevant biotechnology.

8

Feeding the Nine Billion: The Challenge to Society

Florence Wambugu

8.1

Africa Harvest

In this chapter I will focus on the topic of “Feeding The Nine Billion By 2050” and, in particular, on the African challenge. Dr. Raven highlighted this problem very well in Chapter 7, so here I will concentrate on possible solutions to the challenge.

Africa Harvest is a nonprofit, international foundation that has facilities in Washington DC, Nairobi, and Johannesburg. As part of the global community, our foundation believes that is very important for Africa to go forward, and that science, biotechnology and other technologies such as biological pest control and organic farming all have roles to play in Africa in combating the serious problems of hunger, poverty and malnutrition. In this respect, the foundation believes that whilst science is the way forward, it must be intertwined with local knowledge in order to achieve sustainable rural development.

Within the foundation's team, the people are the most important component. The organization provides much interest and support for Africa, and aims to create partnerships with those people who work “on the ground”.

From an international aspect, the foundation is involved with the United Nations Millennium Hunger Task Force, focusing on work with local communities, as well as with the Gates Foundation Science Board, with involvement in bio-fortification and genetic transformation to fortify African foods. Other links include plant genetic resources, the board of CGIAR-IPGRI, the Pan-African network, the Africa Agriculture Development Program, and the Forum for Agricultural Research in Africa. The foundation has also been asked to help develop an initiative in the African Union on how science and technology can help women, especially in Africa. But perhaps the important facet is that of the ground networks, working with the rural communities – because, ultimately, that is where the challenge lies.

8.2

Starvation in Africa

Among the poor of Africa, 50% are farmers living in marginal areas. There are also the landless, the urban poor and the fisheries, but most of the poor are people with small-scale farms who cannot produce sufficient to feed themselves and their families (Figure 8.1). In Kenya, three million of the 30 million population last year went on food aid, a number of these being members of farming communities unable to survive from one season to another.

Although hunger is a global problem, Africa is the only continent where it is predicted that the situation will worsen unless something is done – it cannot be “business as usual” (Table 8.1). It is essential that new ways and new partnerships are developed to find a way forward, because if nothing is done there will be no hope for Africa. That cannot be allowed to happen.

The challenge of feeding Africa is real, and the highlight is the Millennium Development Goal, which focuses on the year 2015. This initiative aims to cut hunger by half, reducing the 200 million hungry people in Africa to 100 million by the year 2015. It seems unlikely that this will happen, because to date very few countries have been able to meet this goal, which is based on Overseas Development Aid (ODA). Committed countries need to provide ODA as 0.7% of their GDP, although only Denmark and a few other countries are currently meeting this goal.

At the G8 summit, the UK Prime Minister, Mr. Blair, devised the Africa Initiative, saying the rich country’s consensus is that they should have an African Marshall plan, reminding us of the international effort to help the tsunami victims. There is in fact the equivalent of a “tsunami” going on in Africa, and if the world were to wake up and decide to do something about the poor in the Africa, they could. Certainly, the Marshall plan is meeting some resistance, but it is hoped that it will proceed.

In Africa, there is also an ongoing challenge of democratization and instability. It cannot be said that the current situation in the Ivory Coast is helpful, but focus must be centered on what needs to be done. There are also the problems of absorption capacity, human infrastructure, and the road networks and infrastructure required to move food aid. The final challenge is access to technological innovation and the practicing of modern agriculture. In fact, the latter is one of the biggest challenges to the rural communities whose interest is to produce enough to feed their families.

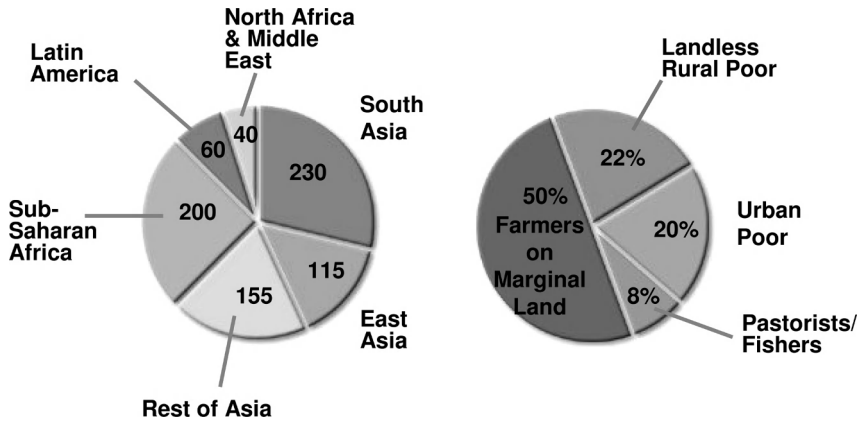


Figure 8.1 Global hunger by region (left) and by social group (right).

Table 8.1 The global distribution of hunger. Africa is the only part of the world where the number of hungry people is currently increasing.

<i>Region</i>	<i>Proportion of world-wide hunger [%]</i>	<i>No. of hungry people</i>	<i>Trend</i>
India	29	232 million	Decreasing
Sub-Saharan Africa	25	200 million	Increasing
China	14	112 million	Decreasing
Elsewhere Asia/Pacific	19	152 million	Decreasing
Latin America & Caribbean	7	56 million	
Near East and North Africa	5	40 million	

8.3

Food Costs

Another issue that is rarely considered in developed countries is the cost of food. In developing countries, the urban population spends most of its money on food, whereas in Europe it is estimated that affluent families spend only 25% of their income on food. In the United States, this figure is only 12%, with the remainder of the money being invested in luxuries.

In Africa, the urban population – which also supports many people in the rural communities – spends most of its money on food. But here it is a vicious cycle, because whether people live in the rural areas or in the urban cities, they are poor because there are so many poor to support.

8.4

Resources Management

The other main challenge is that of natural resources management. This subject was highlighted by Dr. Raven in Chapter 7, and refers to the sustainable use of biological diversity, and the exploitation of natural resources, rivers, forest and mountains. In Kenya, there have been fierce tribal clashes based on water supplies, with one tribe fighting another over water because the rivers and the forests are drying up. There must also be sustainable use of the minerals and oils to develop economies. Although some African countries do have oil reserves, rather than that oil being used to develop the economy it is somehow exploited and does not help in the development of agriculture. This is yet another challenge, because discovering oil in an African country does not necessarily mean that this will be followed by sustainable development.

Environmental protection to avoid climatic change represents yet another ongoing challenge to Africa that must be considered, with the maintenance of water resources, prevention of pollution and the effects of over-exploitation of forests and farming in catchment areas. Today, in some areas people are cutting down trees in an attempt to increase their agricultural production, but the women must then travel far and wide to seek water supplies.

8.5

The Aims of the African People

Perhaps the primary question is what Africa itself is considering about the situation. What do the African people want? Even the African leaders are tired of the situation they are in, and are thinking that it is indeed a long journey of many small steps. Recently, Pan-African institutions such as the African Union were instigated and, for the first time in June 2004, at a meeting in Ethiopia, the African countries came together to elect their first African parliament. This will be stationed in Johannesburg since South Africa, after coming out of apartheid, has become a very stable country in terms of governance and financial power, and now wishes to stabilize the rest of Africa. Hopefully, the role of the African Union will prove fruitful; for example, it recently intervened in the small African country of Togo where, when the president died, his son took over and pronounced himself president. The African union intervened, saying that there must be elections. So, progress is being made. There is also a NEPAD (New Partnership for African Development) peer review, which is bringing some kind of democracy as the countries are made to account for the funding, to account for the way they are governed, and to account for elections.

8.6

African Trading Links

South African economic and political leadership demands the democratization of Africa and stabilization of key troubled countries such as Sudan. The present headlines highlight the case of Darfur, but the Sudan government recently signed an agreement in Kenya and in Nairobi to bring peace to the region, though this has not yet happened. Somalia, another large African country has a government made in Kenya, so something is happening.

The other major issue which might change things in Africa is that of regional blocks. For the first time, Africans are now trading with Africans, whereas previously many African countries traded only with their former colonial link. This situation is changing, with the initiation of ECOWAS, a trading block in West Africa, where the countries share many of the challenges of the environment, and of food supply. Likewise, the South African countries have SADC, which is the South African regional block, while east Africa has the East African Community (EAC) and central Africa has COMESA. There are, in fact, increases in regional block and trade within African countries, and this will greatly assist issues such as GM food which is not exported to Europe but is used to feed the rest of the African continent. South-South trade is also on the increase, as is trade with China, India, Brazil, Argentina. Moreover, there are many treaties being signed on preferential trade between South Africa or other African countries, and this previously very weak link is now strengthening.

8.7

Networks

Today, networking has, for the first time, enabled African countries to share their resources, their expertise, and their limited laboratory space. For example, there is the Forum for Agricultural Research in Africa, FARA, which is 42-African countries network, and there is the Association for Strengthening Agricultural Research in Eastern and Central Africa, ASARECA, with 10 African member countries. At last, something positive is happening and all is not lost. Today, most African countries agree that agriculture will remain the “engine” of economic growth. There is no question of how Africa will grow, with some countries having oil or minerals, while agriculture remains as the engine of economic growth, fuelled by science and technology.

The key African players in this scheme include the African Union, which focuses on international trade and has undertaken the negotiation for fair trade. In that way, each country gets value from their coffee, cocoa and tea. The NEPAD is continuing with the comprehensive Africa Development

Program, whilst FARA is continuing with the scaling up of success models of cassava and the new rice for Africa. The Consultative Group for International Agriculture Research (CGIAR) centers are also contributing their part in bringing high-level research, and are beginning to form strong networks. Bilateral donors are involved, and although the private-sector organizations are still trying to identify their role, the situation is also open to private, local, and international initiatives.

8.8

The United Nations Task Force Strategy

The United Nations Task Force strategy was started after the World Summit in Johannesburg, and has been at the forefront of how immediate action can be taken. The focus here is on 2015, and the immediate action plans developed for Africa are illustrated in Figure 8.2. The first point is the school feeding program, which utilizes locally grown foods and is highly innovative. It is believed that by growing foods with the issue of local preference, money will be brought back into the local economies, the schoolchildren can be fed, and the school can be kept open for use by vulnerable communities, single mothers or nursing mothers, as a feeding place. When children come to the school to eat, many will enroll for lessons. So, the school feeding program, with locally grown foods, will be the highest priority. “Local” food means that it can be obtained from neighboring countries rather than from international sources, unless it cannot be found locally.

In the past, infertile soil and soil depletion have represented major problems in Africa. Consequently, the task of increasing soil fertility will involve a multitude of approaches, including organic or inorganic fertilizers, agro forestry and increasing irrigation. With the exception of Egypt, the African countries do not use their water efficiently, with a large proportion flowing directly into the seas and poor use of river waters. Hence, this represents the major means of increasing food production in Africa. The next point is the use of improved plants and livestock, and that is where technologies such as

- School feeding program with locally grown food
- Increased soil fertility
- Increased irrigation & water management
- Use of improved plants & livestock
- Access to markets (internal, regional & international)

Figure 8.2 The United Nations Hunger Task Force strategy.

genetically modified crops, improved crop by breeding and better livestock, are involved. The final point is access to markets, since by utilizing internal trade rural communities will be able to feed themselves.

8.9

Crop Productivity

Opportunities to increase productivity are manifold (Figure 8.3). In Africa, crop protection is poor, with 40% of the yield being lost to weeds, insects, pests and diseases. It is in this area where technologies such as Bt crops can play a major role. For example, herbicide tolerance would free the African women from the back-breaking task of weeding, while drought-tolerant plants (which several companies claim to have developed) would greatly help yields. Many of the problems of hunger and famine in Africa are the result of drought, mainly because irrigation schemes are not being introduced, and so drought-tolerant technologies achieve major importance. In terms of nutrition improvement, CGIAR is currently focusing on the selection of plants, since it is vital not only to increase the yield of food but also to improve its nutritional value.

The diversification of food is also important, to increase the use of traditional foods, yam, sweet potato and sorghum that have been abandoned. Furthermore, there is a clear need to increase and diversify into cash crops. Today, many African countries are dependent upon only a few crops such as coffee, tea and cocoa, and they need to diversify, for example into the areas of flowers and horticultural fruits. There is an excellent example in Kenya, where small-scale farmers are able to export their French beans to Europe by partnering with large companies.

When considering the year 2050, there is still much to do. Perhaps the primary demand is for creative, community-focused strategies, since no matter how many international initiatives are proposed, they must eventually function

- Crop protection against weeds, insects, pests & diseases (40 % of yield loss)
- Drought tolerant crop varieties
- Nutrition improvement
- Increased use of water
- Increased soil fertility & use of fertilizer
- Diversification of food base
- Increased use of traditional foods (yams, sweet potato)
- Cash crop diversification (flowers, fruits)

Figure 8.3 Opportunities for increased agricultural productivity.

successfully where the poor people live. This is the challenge faced, because many schemes simply will not succeed when they hit the ground. It is important to learn from previous mistakes, and not to repeat them. A more local engagement and openness to the indigenous communities is needed, the important point being to build a futuristic infrastructure and a corresponding distribution system.

8.10

Private Sector Initiatives: The Case of TC Bananas

I would like to close the chapter by showing an example of a private sector initiative. I believe that companies must look at Africa as a future market. Today, although the main topic of conversation is China, Africa is clearly the next biggest market, but it has not been tapped. A brief story may help here. One of the largest companies in Africa today is Bata, a Canadian company which came to Africa before colonization. The Bata salesman aimed to identify markets for shoes, but one salesman – on seeing people with animal skins and no shoes – maintained that there was no market because nobody wore shoes. But another salesman recognized that as nobody in Africa had any shoes, this was an excellent opportunity. There were young people who could be trained, and there were the skins needed for shoes. Bata decided to focus on people without shoes, and today the company still does that. The first shoes I wore when I went to secondary school were from Bata. Today, they do not compete with Italian leather, but instead focus on people without shoes.



Figure 8.4 A typical family in Chura living on 0.2 hectares of land and receiving food aid.

So, they are making major sales in Africa, and that is the attitude that the private sector needs to adopt.

In a photograph of a typical Kenyan family with many children (Figure 8.4) the father will be absent because he feels ashamed of his family as he is very poor and cannot afford to buy many goods. Currently, the DuPont company has decided to support the Chura community, where the photograph was taken. The company has no commercial interest but simply wants to learn. There are no well-evolved models from which the private sector can learn to enter this market, so DuPont has decided to fund the project, taking corporate social responsibility in caring for the poor and sponsoring the application of agricultural technology, ensuring good agronomic practice and helping with access to the markets. This holistic approach to sustainable agricultural development is termed the “whole value chain”. This is also DuPont’s company strategy, which Kenyans will also learn to use.

The aim of the project is not to promote DuPont’s products, but rather to help the community in areas about which they know very little, or in which using Africa Harvest as a partner can help. The goal is sustainable rural community development through increased banana production to alleviate hunger, poverty and malnutrition. This three-year scheme – which was started in 2004 – does not utilize GM technology (not that there is anything wrong with GM methods). Instead, it uses tissue culture (TC), whereby the bananas are improved in terms of their having no disease (Figure 8.5). The production of a pioneer hybrid has demonstrated that good agronomic practice can also produce good yields. The participation target is about 60 000 to 100 000 people – that is, 6000 families each with an average of 10 members.

The project is under way, and will be allowed to evolve. Within the project there is technology, good agronomic practice, water, manure, integrated pest management, and overall project management. This technology can add substantial value to the product, and has already doubled the harvest from a single banana sucker, from 20 to 40 kg (Figure 8.6). The data shown in Figure 8.7 show that the input for the tissue culture and non-tissue culture systems is similar. However, the technology provides great value – which is essential for Africa – by creating increased production for the same area of land. The initial peak for costs relates to the purchase of equipment, but once bought this will last for many years. It is in this way that sustainable development can be brought about.



Figure 8.5 Raising banana seedlings from tissue culture in the Chura project.

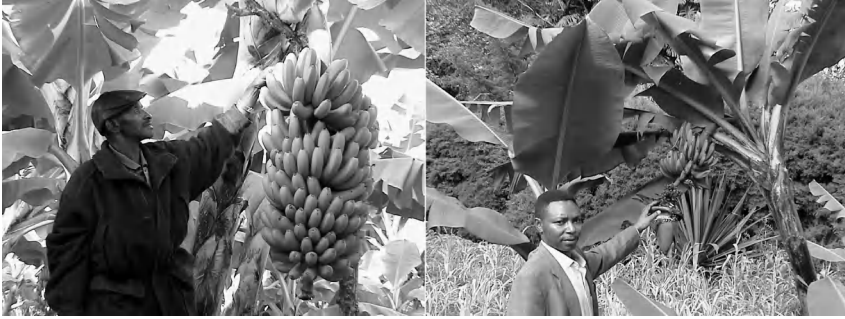


Figure 8.6 Increased harvest from a tissue culture sucker (left) versus a sucker from a traditionally grown banana plant (right).

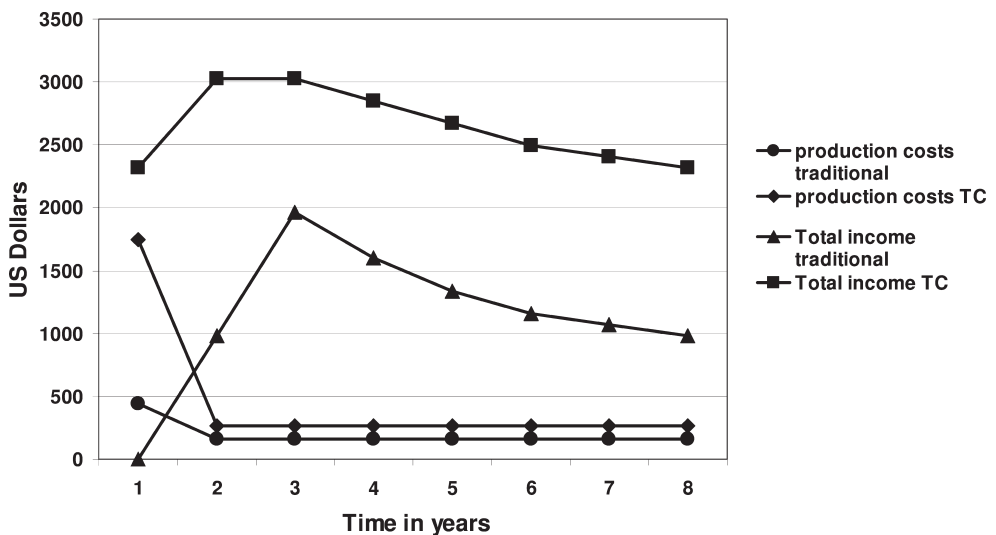


Figure 8.7 Production costs and revenues associated with traditional and tissue culture (TC) banana orchard management.

8.11

The Whole-value Chain Approach

I believe that the extension service to the poor cannot be the traditional extension service of old – that is, to provide them with some information and to stay with them through the value chain all the way to awareness creation, baseline studies, and understanding the community (Figure 8.8). The next step is to identify where the improved seed can be found, be it banana or maize. The third step – which represents the main challenge – is to achieve

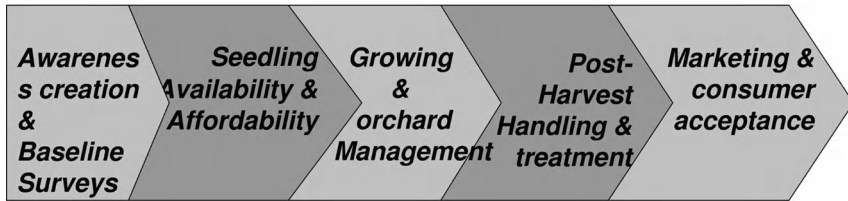


Figure 8.8 The whole value chain approach.

good agronomic practice in terms of orchard management, water and manure supplies, and IPM. The next stage is the post-harvest handling and treatment of the crop; this can involve major product loss (with perishable fruits such as banana or papaya, this can reach 40%) and, therefore, loss in income. The final stage is that of marketing, value adding, and feedback.

This approach must be conducted in the way that companies do business. When the plant is obtained from the laboratory, there is a requirement for education, training and knowledge transfer – and these cannot be provided by traditional extension. The communities need to know, to ask, to understand, and they need to see how the scheme fits into their own system. So, engaging the community is an absolute *must*. This goal cannot be achieved in a day – in fact, on average it takes about three months to complete. The final target is for the community to identify a source for the seedlings, and to determine that are they certified, they are disease free, and that they are vigorous.

The outcome of a successful scheme is a well-managed orchard that will last over ten years. The product can be harvested every six months, so the small orchard then becomes a small business, because the fruit can be eaten and also sold to create income and provide investment. When working with the community, it is important that they appreciate the difference between the traditional system and tissue culture technology, as the advancement must happen *with* them, and not *for* them. Only then will it change peoples' lives and create excitement as they see it happen.

Finally, by the time the product reaches the supermarket it has made a large profit for the community. In fact, every dollar invested by the community will produce three dollars in return. That is a kind of business model that is going to turn poverty around. Lastly, one major advantage would be to engage the youth of the community, many of whom want to be entrepreneurs rather than farmers. So, we tell them that farming is a business, hoping that this will boost their excitement because they *will* become entrepreneurs.

Author Biography

Richard Flavell

CSO, Ceres (US)



Dr. Flavell joined Ceres in 1998. From 1987 to 1998, he was the Director of the John Innes Centre in Norwich, England, a premier plant and microbial research institute. He has published over 190 scientific articles, lectured widely and contributed significantly to the development of modern biotechnology in agriculture. His research group in the United Kingdom was among the very first worldwide to successfully clone plant DNA, isolate and sequence plant genes, and produce transgenic plants. Dr. Flavell is an expert in cereal plant genomics, having produced the first molecular maps of plant chromosomes to reveal the constituent sequences. He has been a leader in European plant biotechnology initiating and guiding a pan-European organization to manage large EU plant biotechnology research programs more effectively. In 1999, Dr. Flavell was named a Commander of the British Empire for his contributions to plant and microbial sciences. Dr. Flavell received his Ph.D. from the University of East Anglia and is a Fellow of EMBO and of The Royal Society of London. He is currently an Adjunct Professor in the Department of Molecular, Cellular and Developmental Biology at the University of California at Los Angeles.

9

Feeding the Nine Billion: The Challenge to the Marketplace

Richard Flavell

9.1

Introduction

In this chapter, I will address the role of the industrial sector in relation to the target of feeding nine billion people by 2050, and attempt to envisage the situation at that time. In addition, I will also outline some of the science base and progress that is envisaged by all, and which will inevitably take place in the intervening years to achieve the goal.

In 2050, there will be many people living in the well-developed richer countries who will certainly have food enough and, as is the case today, there will be many of us in the United States and Europe who choose not to have the healthiest of diets. It is well known that these large increases in population will occur mainly in those countries characterized today as housing the poor, and where in 2050 a shortage of food will surely still be the case. This is not pessimism, it is realism. Although malnutrition is rampant amongst such a large fraction of the people on the planet today, it could be even more widespread in 2050, and perhaps even in places where there are sufficient calories available. Again, this is not pessimism, it is realism. By 2050, energy and water will be expensive because they will be scarce commodities, given all of the pressures on those resources on the planet. So, what changes will be needed in order to feed nine billion people? Clearly, there will be a need to increase sustainable productivity per unit area of land everywhere. We must learn not to rely on high levels of inputs, and we will have to conserve water and energy. We will also have to feed the urban poor, with relatively fewer farmers being involved. Surely, food will have to be made healthier and more nutritious, and many people will probably need to gain access to more diverse sources of food. There will also be the problem of generating supply chains that are economically sustainable (Figure 9.1).

- Increase sustainable productivity per unit area of land
- Produce increases with few inputs
- Conserve water and energy
- Feed the urban poor with fewer farmers
- Make food healthier and more nutritious
- Create more diverse food sources, to provide better nutrition and reduce security risks
- Ensure that supply chains are economically sustainable

Figure 9.1 Necessary agricultural improvements in the poorer countries.

All of these topics are frequently discussed by companies today, both in the developed countries and the developing countries. One frustrating point here is that, inevitably, all of these proposals are of a very general nature, yet there is so much diversity in the world, and the solutions will have to be found on the ground, often from the bottom up. So, whilst many thousands of solutions will be proposed to feed the population of 2050, I believe that no matter what is done on a global scale, local production will still be a very important issue.

9.2

Industrial Sector Involvement

It is unclear, when referring to the industrial and public sectors in 2050, exactly what these will be. When using the term “industrial sector”, I am not referring to today’s multinational companies, as many of these may well have disappeared by 2050. In fact, by then the industrial giants may be operating from China, Mexico and Brazil rather than the United States and Europe. However, there is certainty that then, as now in the developed countries, industry will dominate the food supply systems at every step in the business. But why might this situation change? It is because there are very many signs that in Asia and Latin America, and in parts of Africa and across many other regions of the world, the private sector, the will and the drive to be entrepreneurial is growing rapidly. So, it can be assumed that, by 2050, there will indeed be a very strong industrial sector associated with food production in many parts of the world where they are not instantly recognized today. In my opinion, this will be the major market change during the next 40 years. Companies must be driven by profitable markets, and it cannot be assumed that the whole world will be a profitable market in 2050. Co-governmental multinational agencies of various types will still be essential to provide food for the poor in many parts of the world, and especially in Sub-Saharan Africa, no matter how much entrepreneurial enthusiasm surfaces during the next 20 years to influence the situation in 2050.

The interaction between what is known as the industrial and the public sector through regulation and macroeconomics, microeconomics, taxation, must continue to be mutually supportive, and I believe that the pressures will be such that they will have to become even more mutually supportive for profitable and non-profitable crops around the world. There is much behind that statement, although of course it is too complex to justify at this point.

The final point to be made is that the one thing that industry can do, does do, and will need to do, is to continue demonstrating how to progress from science to production and marketing. This is not well understood in the academic or scientific communities – and actually is not particularly well understood in other types of organization connected with the research and development of food production. Of course, the ways in which such progression is achieved are culturally very diverse, and so there is much to be learned there. However, this industry will be increasingly scattered around the world and will surely become that type of role model. Although industries must be driven by profitable markets, they also want to make large profits so that they can plan for the future, which in turn means investing in research and development, and in sales and marketing to create new and better products. And if companies plan for their future they will need to increase their market share by creating a better product – that is, a product which is more popular among consumers than those of their competitors. So, it is new and better products that drive industries, and of course this is an essential component of the task to feed the world by 2050 – new and better products worldwide.

Industries also focus internally on improving efficiency while reducing prices. Even in the research sectors of today's agroindustries, much emphasis is placed on how the cost to a data point can be reduced in a plant-breeding program. In this way, the industries can be seen as role models for turning scientific discoveries into products, for making production more efficient, for reducing costs, and also for increasing environmental sustainability. The latter point is clearly on the agenda of industries for the future, because in addition to producing better, more saleable products, the goods must be matched to consumer needs, and this must be achieved with the resources available. Industries invest huge amounts of effort in succeeding in this respect, and it is likely that much of this effort will have an impact on the design of agricultural crops for the future.

We are all familiar with wide diversity of industry in food production today, from conceiving which new types of plants should be available, through seed multiplication and distribution, supplying fertilizers and disease control chemicals, overseeing the machinery of transport systems, and food processing (Figure 9.2). It is also known that, in regions where the poor live, these facilities are either absent or are in very short supply. But surely, by 2050 some of these gaps will have been removed.

- Plant Breeding of profitable crops
- Seed multiplication and distribution
- Fertilizers, disease control chemicals
- Machinery for harvesting
- Transport, storage, processing, distribution, marketing, retail
- Food processing

Figure 9.2 Roles of industries in food production.

In this respect, the goals for agriculture include increasing yield potential, closing the yield gap between what is known to be possible and what the average farmer achieves, sustaining current yields, and enhancing nutritional properties. These items of importance are exactly the same in the private sector as they are in the public sector. In other words, there is a universal common agenda. Today, when we see what must be achieved to increase yield potentials and enhance nutritional quality, we know that biotechnology, and the genetics of plants in a broader sense, will make an enormous contribution. There is no doubt in my mind, based on currently available information – and what will emerge during the next 20 to 30 years – that what we now recognize as the ceilings for crop production will be vastly increased by modifying the genetic contents of these crops. Indeed, there is great optimism that the scientific pace at which we are learning about the underpinning of crop productivity will be merged fairly rapidly into crops, including those which, as yet, have not received attention from research scientists. I have no doubt that a comprehensive set of traits will become available that will address many of the issues of sustainability in relation to managing and coping with environmental difficulties, as well as sustaining the quality of the soils.

9.3

Nutrition and Genetic Modification

Today, it is also very clear that the nutritional shortfall of cereals, for example, leads to malnutrition, even in those people who have an adequate calorie intake. These shortfalls can – and surely will – be overcome by genetic modification, and there is a plethora of methods emerging today that will make the processes of plant breeding much more rapid, including the control of recombination. I predict that on this time scale, what is currently regarded as biotechnology, and what will be achieved during the next 20 years, will transform the science base for improving productivity and sustainability in

the agricultural sector. On this point, today it is known that globally, 23% of humans obtain their calorie intake from rice, 17% obtain it from wheat, and 9% from maize. Currently, these three crops have a major impact on feeding the world, and that situation will surely be the same in 2050. Today, rice, wheat and maize are the subject of huge investments in research and development in the industrial sector of the west, as well as in national programs in the poorer countries. There is a common research base here, a common agenda, and a common set of goals. There is adaptation to different environments locally, although the broad agenda is very much the same, and a great deal of optimism should be taken from that. There is indeed a global research base addressing the needs of both the rich and the poor.

By 2050 – and perhaps before that time – it is very likely that every gene and most common variants of every gene in all major crops and many minor crops will be known. These advances will have been achieved because DNA sequencing will have become so cheap and easy to perform, and so universally employable because of the needs for human genetics, the human genome and all other topics related to public health. As a consequence, breeding will be conducted based upon known genes, gene combinations, and their role in the desired traits. In recent years there has been a tremendous increase in what is known as comparative biology, because there is now an understanding of the genetic relationships between species and between crops, and this allows knowledge of genes and genes systems to be combined across the plant kingdom – and perhaps even further than the plant kingdom. This knowledge base is extremely useful and very powerful, and plant breeding both today in well-equipped laboratories – and certainly in 2050 – will be inspired, governed and managed very much by the products of the information technology industries and databases from public and private sector sources. This represents a huge change in the ability to have access to and to exploit the knowledge base that underpins agricultural productivity and which simply did not exist 20 years ago. There is also the range of opportunities that will be derived from knowing the value and power of individual genes to overcome deficiencies and to facilitate relatively easy breeding, using GMOs. There will also be factory systems that will most likely be very much more advanced than anything known today for managing these programs through interactive software and robotics.

I am not trying to paint a fanciful picture; rather, I am trying to confirm that there is no reason why this will not be the way in which plant breeding is approached long before 2050 in many parts of the world. It will certainly be encompassing what are known today as minor crops, and the justification for this is the data available today. Clearly, the vision and directions of both the private and public sectors, combined with the new knowledge base and specifically trained people, will create an ideal opportunity to transform the germplasm in order to fulfill these needs.

9.4
Genetic Manipulation

The most important factor required to achieve the target of feeding the nine billion is that of continued investment. Visionary people are also needed who are prepared to commit resources to the science base. This situation is not hopeless, it is in fact deliverable, and the opportunity should not be lost. Increasingly, crops will be identified by their appearance in the field under different environmental stresses, the taste of the product, and their chromosomal appearance, nucleotide by nucleotide, gene by gene. The confidence behind these statements is based on events occurring in the company for which I work, Ceres. This is a tiny company that has worked for only a few years in this area, yet we know rather precisely the specific genes which, when changed in a plant, will alter a long list of characteristics (Figure 9.3).

Moreover, these are the types of characteristic which must be changed in a breeding program and, given that there are many thousands of such research investigations being conducted worldwide, there is no question that making these changes is within our reach. Some of these changes are illustrated here. Figure 9.4 shows a rice plant with a high rate of photosynthesis such that a greater biomass is produced. Figure 9.5 shows plants that have been exposed to drought and then watered; the parent plant cannot revive, but the one with the additional gene revives very well. Figure 9.6 shows rice plants which have been heat-stressed; the parent plant shows signs of stress with the leaves not recovering, whereas the plants which have received a gene from either *Arabidopsis* or maize survived well. Further evidence is shown in Figure 9.7,

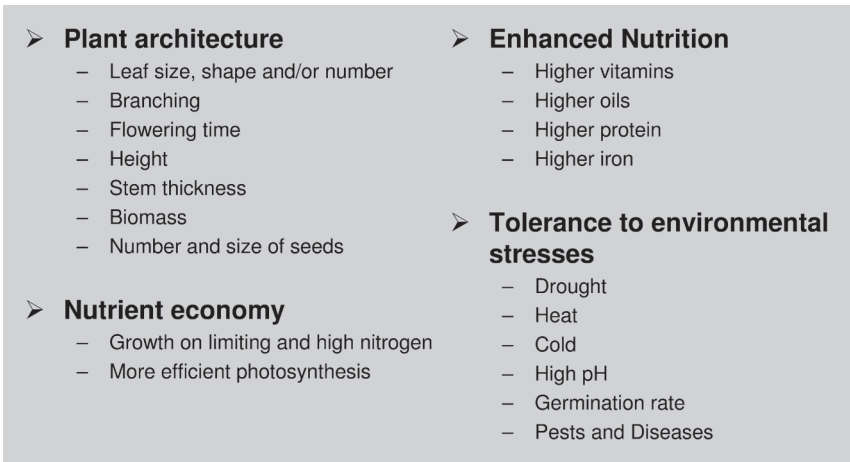


Figure 9.3 Potential for crop improvement through genetic engineering. Listed are genes discovered by Ceres that code for agronomically interesting traits.



Figure 9.4 Increased biomass from increased CO₂ capture. The engineered rice plant on the right is able to carry out photosynthesis more efficiently than the wild-type plant on the left.

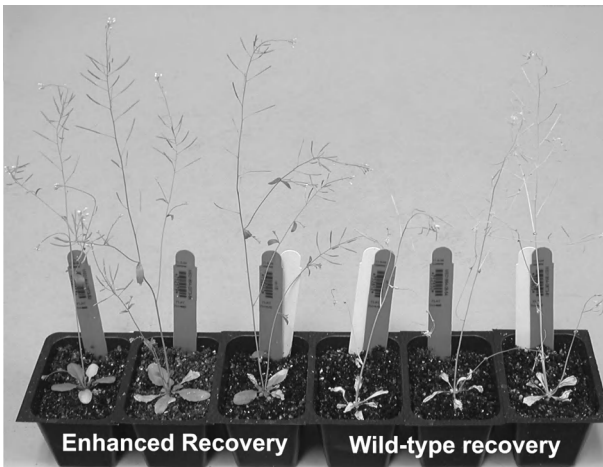


Figure 9.5 Enhanced recovery from drought in plants that carry an additional gene inserted by genetic engineering. The mother plants are shown for comparison on the right.

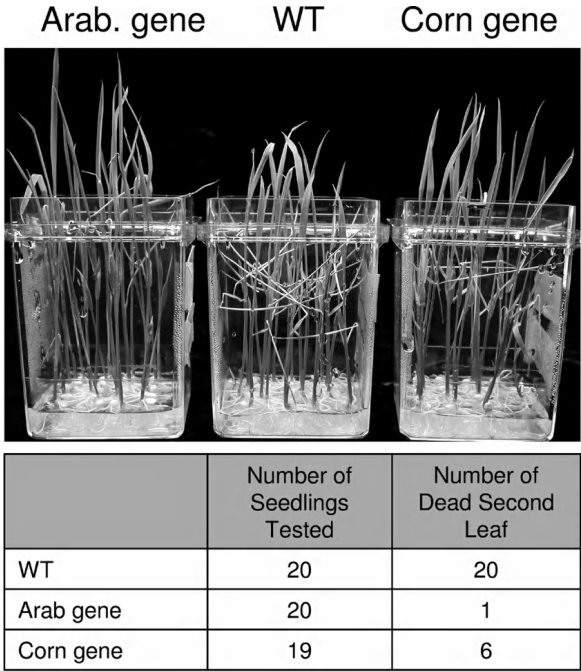


Figure 9.6 Rice plants subjected to heat stress are recovering well if they carry an additional gene from *Arabidopsis* (left) or from maize (right).

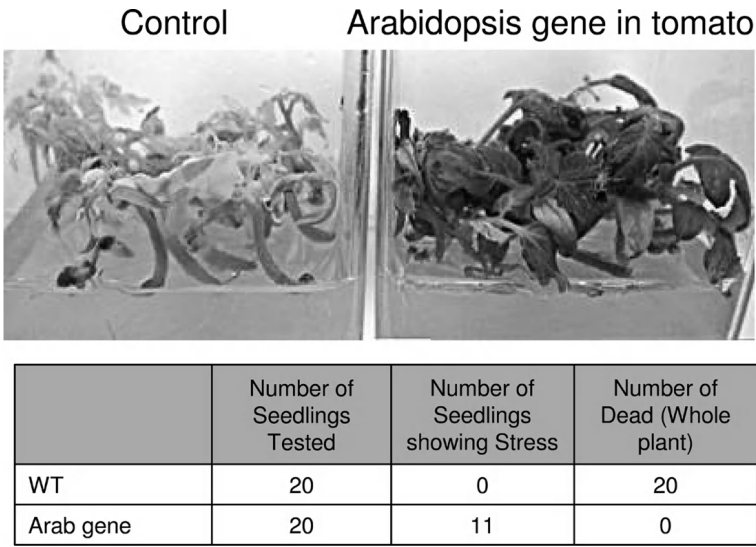


Figure 9.7 Tomato plants subjected to severe heat stress recover if they carry a gene from *Arabidopsis*.

where a heat-stressed tomato plant carrying a gene from *Arabidopsis* recovered well. Clearly, this knowledge base also traverses species!

The rice breeder of today is assisted by the *Arabidopsis* scientist, as is the tomato breeder, the wheat breeder or the corn breeder. This knowledge base saves vast amounts of time and effort, and will in the future be extremely influential in speeding up the pace to address many of the issues that are so important in producing a sustainable agriculture. The “plug and play” concept of genes, though easily overestimated, should not be underestimated, because it means that many plant scientists who do not see themselves as addressing the world food problem are in fact doing so. This is because the genes they are discovering, and the role that those genes play in specific traits, can be utilized by the private and/or public sector. Increasingly, when breeders start from a knowledge base derived from genomics – and whether the gene systems occur naturally in the crop or are present as transgenes – they can utilize gene combinations and develop a range of products with a directness and a predictability that, hitherto, has not been possible.

Today, the biotechnology practiced today within academia, in companies and in major international institutes, is directly associated with DNA sequencing. Many of the enzymes, reagents and polymerase chain reaction systems have been obtained via private sector investment, usually in small entrepreneurial companies (Figure 9.8). So, the importance of an entrepreneurial research base should not be forgotten, especially in the areas of healthcare and plant breeding. These advances will surely continue during the next 20 to

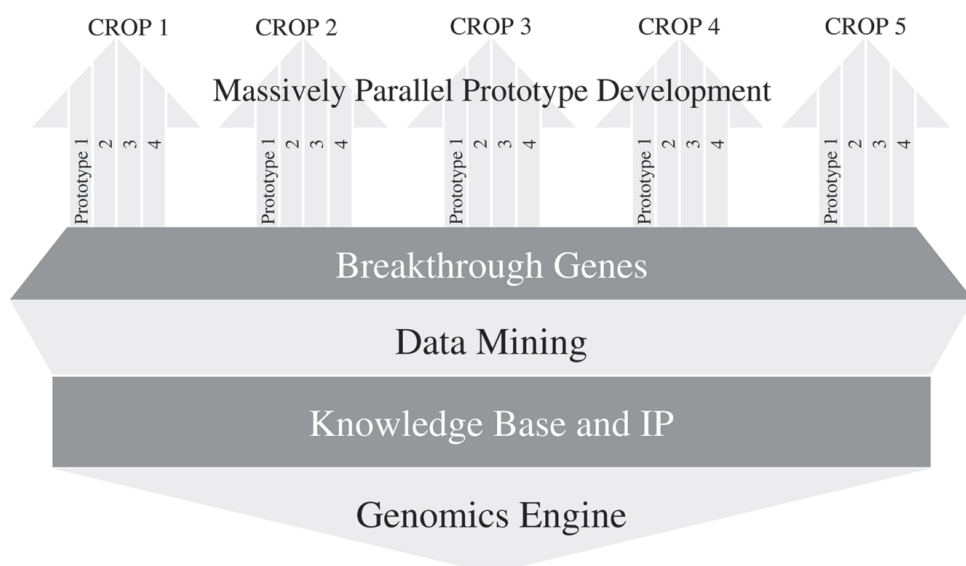


Figure 9.8 Genomics-driven product development in industrial crop science.

30 years, and the entrepreneurial base, together with its investments, will undoubtedly make very important contributions to this new agriculture.

9.5

Public–Industry Partnerships

To conclude, I would like to highlight some points about public–industry partnerships. Much has been said on this topic, and many have suggested critically that such partnerships do not occur. But I am one of those who feels anxious that there are insufficient public–industrial partnerships, because they will be essential if the goal of feeding the nine billion is to be met. The differences between these partners are often emphasized, the criticism being that industry will only become involved where there is a profit to be made. Yes, there *are* many differences – industry is driven by markets – but we should perhaps consider what the partners have in common, and that is that both groups, wherever they are in the world, have as a common interest consumers who they want to satisfy. Both parties seek to enhance the purchasing power of everybody concerned, but industry is interested in understanding new markets and opening them up, as was mentioned by Dr. Wambugu in Chapter 8. In fact, many of the innovations of the industrial sector, for example the progression from science to a product, cost reduction, automation, and increasing efficiencies, can – and should – also be learned by the public sector.

In summary, it is likely that by 2050 the genes of all important crops, whether major or minor, will have been sequenced and genetically mapped as routine, with automated systems facilitated and driven by industry and the public sector. I am not making the assumption that the driving force will continue from the same industries as known today, as many more industries are being started, and many more surely will succeed. However, I believe that there will be international centers serving local needs in germplasm characterization and selection on a scale and with a vision that is perhaps very different from what is characteristic of the Consultative Group for International Agriculture Research (CGIAR) today. These international centers may be inspired by Beijing or Sao Paulo or other places, but they will be very efficient – and they will need to be. In plant breeding the area of genomics is straightforward, for many reasons. The difficulty comes in assessing the characteristics of the plants when they are grown in the fields, and in the environments, because in order to guarantee the necessary progress this must be carried out on a larger, more extensive, more localized pattern than is done today.

9.6

Intellectual Property

The final point to be made is that of intellectual property. This very complicated issue is on the minds of many with regard to the private sector and industry. In Chapter 5, Dr. Potrykus suggested that when the project was right, industries would be prepared to donate or to come to some arrangement over intellectual property. However, with regard to feeding the world by 2050, this might be somewhat of a red herring.

9.7

The Way Forward

What, then, is the way forward? As a scientist, I should perhaps be emphasizing the opportunities that plant biotechnology can provide to meet these needs by 2050, and attempting to convince the world that science will provide options to feed the nine billion. However, if the anti-science vote continues to disrupt funding, and to deter young people from an enthusiastic entry into science, then life will be much more difficult. So, we must work hard to convince the world that the science base will provide the options, and then tell everybody the news. It will be important to win the public's confidence, to say not only that it is possible but also how it will happen, and what the course of action will be.

The industrial sector serves as the powerhouse of knowledge, and this must be tapped to address the problems of product development for the poor. It is also clear that none of these advances will be made unless we can inspire the political, social, economic, trade and investment climate worldwide to help open up the markets, and to give confidence to industry and the public sector to aspire us all to meet these needs of humanity in a global context. How do we inspire these political, social and economic aspects? It is very difficult, very complex, and clearly it must be done in a myriad of ways, and in a host of countries and local environments. However, unless that vision is maintained for a large number of people, year in year out, it will be difficult to reach the goal of feeding nine billion people.

Today, education is seen as a key element by many. The whole process of education and training to bring people familiarity with the systems, and to provide opportunities and investment is absolutely key, and must be grasped vigorously and enthusiastically at every opportunity. To me, the opportunities and the challenge are exciting, because we must sell this exciting "biovision" of what the possibilities are – and indeed the opportunities for creating sustainable supplies of good food for all by means of sensitive science and technology. This is a huge agenda, but I feel that the industries of today and

tomorrow are ready to tackle the challenge, especially where investment climates are right and the learning process has been taught. Science and technology has much to offer, and the world must be convinced that it will provide these options.

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Key Messages

Author Biographies

Mike Gale



*Member CGIAR Science Council & John Innes Foundation Emeritus Fellow,
John Innes Centre (UK)*

Professor Mike Gale recently retired from his position as Associate Research Director at the John Innes Centre in Norwich, UK. He started his work on wheat genetics at the Plant Breeding Institute in Cambridge in 1968 and is best known for his research into dwarfing genes, pre-harvest quality loss and the development and application of molecular genetic markers. His group made the first comprehensive molecular map of wheat and reported the first observations that indicated that grass genomes were much more conserved than previously thought. The development of the ensuing comparative genetics (synteny) paradigm has been acknowledged by the award of the Rank Prize for Nutrition in 1996 and the Royal Society Darwin Medal in 1998.

Prof. Gale received his BSc in Genetics from Birmingham University in 1965 and his PhD from the University College of Wales at Aberystwyth in 1969, by which time he had already moved to the Plant Breeding Institute. He became Head of the Cereals Research Department in 1986 and, in 1992 after the institute had moved to Norwich as the Cambridge Laboratory, he became Head of the institute. When the Cambridge Laboratory merged with the John Innes Institute and the Nitrogen Fixation Laboratory to form the John Innes Centre in 1994, Prof. Gale became a founder member of the Management Board. He had a brief spell as Director of the John Innes Centre in 1999. He was also appointed to a John Innes Professorship, held at the University of East Anglia, in 1999.

Prof. Gale has sat on several key panels, including recent UK GM Science Review Panel (2002–2004), the Scientific Advisory Committees of the Rockefeller Foundation's 'Rice Biotechnology' (1989–2000), the Nuffield Council on Bioethics Working Party on Genetic Modification in Plants (1997–1999, 2002–2003), and the Board of Trustees of the International Rice Research Institute in

the Philippines (2001–2004). Much of his time is now devoted to the CGIAR Science Council to which he was appointed a Member in 2004. His other ongoing commitments include the Advisory Board (Fachbeirat) of the Max-Planck Institute for Chemical Ecology in Jena (1997–present) and the Scientific Advisory Committee for the Rockefeller Foundation's Program on 'Biotechnology, breeding and seed systems for African crops' (2002–present).

Prof. Gale was elected to the Royal Society in 1996 and to the Chinese Academy of Engineering as a Foreign Member in 1999. After his retirement he was appointed as John Innes Emeritus Fellow at the John Innes Centre and as Professorial Fellow in the School of Biological Sciences, University of East Anglia. He has published more than 200 scientific papers.



Raymond C. Offenheiser

President, Oxfam America

After working in developing countries for more than 20 years, Raymond C. Offenheiser returned to the US in 1995 to join Oxfam America as its President. Oxfam America, a Boston-based international relief and development agency, supports organizations committed to developing solutions to poverty and injustice in more than 30 countries. Oxfam America is the U.S. affiliate of Oxfam International – a confederation of 12 Oxfams which collectively work in 120 countries, and have an annual revenue of more than \$500 million. Oxfam compliments its grassroots work with far-reaching programs to engage world public opinion and influence decision makers on behalf of people living in poverty, and as such brings a unique and informed perspective to issues that affect the world's poor.

Under Mr. Offenheiser's leadership, Oxfam America has more than doubled in size in less than 6 years, and has repositioned itself as a leading voice on international development and global trade. Mr. Offenheiser has worked his entire career in the non-profit sector, and is a recognized leader on issues such as poverty alleviation, human rights, foreign policy, and international development. He brings more than 20 years of international development experience as a field programmer, grant maker, and executive in Asia and Latin America. Prior to joining Oxfam America, he served for five years as the Ford Foundation Representative in Bangladesh and, prior to that, in the Andean and Southern Cone regions of South America. He has also directed programs for the Inter-American Foundation in both Brazil and Columbia and worked for Save the Children Federation in Mexico.

He serves as a resource and frequent commentator in the media and before diverse public fora on such issues as foreign aid, global poverty, humanitarian relief, international agriculture, human rights, global trade policies and corporate social responsibility. He has appeared in programs on CNN, NPR, and the BBC, and has been a quoted source in the *New York Times*, *Washington Post*, *Boston Globe*, *Baltimore Sun* and other major American newspapers. He

is currently a board member of Oxfam International and Interaction, the association of American international NGOs. He also serves on advisory boards to the Kennedy School of Government at Harvard University, the World Economic Forum, the Aspen Institute, the Asia Society, the World Fish Center in Penang, Malaysia, the World Agricultural Forum and the Kellogg Center at the University of Notre Dame. He is a member of the Council on Foreign Relations. Mr. Offenheiser holds a Masters Degree in Development Sociology from Cornell University and earned his Bachelors Degree from the University of Notre Dame. He speaks fluent Spanish and Portuguese.



F. Guillaume Bastiaens

Vice Chairman, Cargill

Guillaume Bastiaens was elected vice chairman of Cargill in February 1998. He is a member of the Corporate Leadership Team. He also has executive supervision of corporate research and development.

Mr. Bastiaens was elected to Cargill's Board of Directors in 1995, and serves as Chairman of the Business Unit Strategy Working Group and the Technology Committee.

Mr. Bastiaens joined Cargill in 1967 as refinery supervisor of the Processing Division in Amsterdam. He continued in various supervisory positions at Cargill facilities in Europe and was responsible as plant operations manager of the European Processing Group until transferring to Minneapolis in 1981 as vice president in the company's Processing Group, responsible for the operation and engineering of all domestic and international processing facilities. He was elected corporate vice president of Cargill in 1986, responsible for providing overall direction of plant operations and technical development for Cargill. He was named chief technology officer in 1991 and elected president of the Industrial Sector in 1992 and president of the Food Sector in August 1994. He was elected an executive vice president of Cargill in August 1995.

Mr. Bastiaens serves as a director on the board of the Donaldson Company. He is a member of the executive board of SIFE (Students in Free Enterprise), a non-profit organization.

He is a native of Belgium and holds a degree in chemical engineering.

Synthesis and Recommendations

Mike Gale, Raymond C. Offenheiser, F. Guillaume Bastiaens

1

The Parameters

The global situation in agriculture and nutrition can be characterized by several key parameters:

- Agriculture
 - 75% of world's poor are engaged in traditional farming on marginal lands.
 - The available agricultural land is diminishing.
- Poverty
 - 1.2 billion people live on less than \$1/day.
 - 50% of the world's population live on \$2/day.
 - The world's poor spend 80% of their income on food.
- Urbanisation
 - In the urban population, changes in diet lead to an increase in protein consumption.
 - Megacities create increasing requirement to import food.
- Water Use and Security
 - Water remains a precious and diminishing resource.
 - 1 billion people in developing countries have no access to safe water.
 - 80% of the world's water is used for agriculture.

2

The Potential Benefits of Biotechnology

What is the impact that science and technology can make on nutrition and food supply?

- The cost of production per unit and preserve biodiversity can be reduced.
- Resources can be conserved, e.g. by lowering dependence on fertilisers.
- Energy expenditure in poorly nourished rural population can be reduced by decreasing the amount of back-breaking labour.
- Adaptability to environmental stress such as drought and salinity can be provided.
- The nutritional content of food can be improved through biofortification, e.g. in Golden Rice.
- New traits may be transferred to crops relevant to developing countries.
- Better soil management practices such as 'no-till' can be enabled.
- Livelihoods of poor farmers can be enhanced.

To address the needs of poor farmers in developing countries, there must be an increasing investment in R&D capacity in the public sector.

A large part of the problem in ensuring food security is political, structural and institutional. Thus, biotechnology is only part of the solution and taken in isolation cannot adequately address any of these problems.

3

Call for Action

3.1

Regulation of Genetically Modified Organisms (GMOs)

The ideal goal is reasonable regulation, i.e. to regulate traits, not the technology as such and to follow a common sense approach in doing so.

The case of golden rice exemplifies the humanitarian problems associated with GMO regulation.

- Delayed implementation of new crops due to over-rigorous and costly regulation is costing thousands of lives.
- If golden rice implementation had occurred in 2003, assuming only 1% adoption, 65,700 children's lives would have been saved.

While there is a place for biosafety, over-regulation stifles innovation, raises costs and stalls introduction of new products.

- Large costs in financial and human resources are a greater burden for innovators in the public sector and drives commercialisation towards the private sector and away from public institutions and the poor.
- The problem is especially important for farmers in developing countries, because public sector funding will be the most likely to target their needs.

3.2

Education

To reap the benefits of biotechnology, a better education is needed.

- Society must be educated to better understand the scope and potential of biotechnology, not only in agriculture but all other aspects of their lives. There should be a unified perspective on multiple uses of red, green and white biotechnology.
- The general public must be educated about the exciting developments in genomics and its potential to reshape their lives in exciting ways in the 21st century. This discussion reaches considerably beyond agriculture.
- Civil society, particularly in OECD countries, must be engaged in an active and inclusive public discussion of risk assessment for biotechnology.
- Farmers in developing countries must be trained in best practice in agriculture, better crop management and livestock production and must receive information about new technologies.
- We must educate and empower women about advantages of biotechnology; particularly its time and labour saving advantages.

3.3

Communication

To reap the benefits of biotechnology, new ways of communication are needed.

- Society has a distorted perception of risk and is misusing the precautionary approach as a precautionary principle.
- We need to focus on opportunity not risk.
- We need to share fact-based evidence and foster informed decision-making.
- We need to engage in real dialogue to come up with solutions. This is the discursive model.
- We need immediate action – there is no time for ideological arguments.
- We need to combat the considerable erosion of trust in science and governments, as it is critical to improve consumer and societal confidence. The path towards this is open and transparent dialogue.

3.4

Knowledge Transfer and Access for All

Improving knowledge transfer and access to new technologies, databases or germplasm is a difficult challenge.

- Intellectual property protection rights are necessary to spur innovation.
- Knowledge may be overly privatised to the detriment of access, research, and the public sector's ability to participate.

- The conflict between potential humanitarian benefit and shareholder profits must be resolved.
- Transfer of genetic knowledge across species barriers and to locally relevant crops in developing countries must be enabled.

3.5

The Need to Create an Enabling Institutional Environment

How can institutions and global initiatives help in agricultural development?

- Create new institutions to replace the now defunct agricultural extension programmes.
 - New approaches are required.
 - New roles for NGOs in absence of classical extension need to be defined.
- Focus on R&D on crops that are relevant to developing countries.
 - Create markets for seeds relevant to the needs of poor farmers.
 - Strengthen public sector research.
- Build links between public and private sectors.
- Enhance markets for product inputs in developing countries.

4

Market Failures

The global market for agricultural products has severe implications for agricultural development.

- Markets are not sending the right signals and incentives to encourage industry to address concerns of poor countries.
- There is a lack of funding for public goods for developing countries.
 - Research and investment in the public sector is shrinking.
- Investment is skewed towards Northern markets and not delivering for needs of the South.
 - Most research is focused on four crops relevant to the North.
- Market concentration follows a power law distribution.
 - Because of market network complexity; strong players are favoured.
 - Agribusiness and small farmers only capture 13% of profits.

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Module I

Industrial Biotechnology: Hopes, Fears and Challenges

Introduction

*Dominique Lecourt**

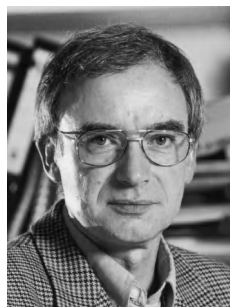
Over many centuries agricultural and industrial activities have greatly modified the medium in which humanity evolves and works. In recent decades the rate and rhythm of the quantitative and qualitative changes which seriously affect the structure and the functioning of the biosphere has constantly accelerated. It naturally follows that there has been a corresponding increase in pollution, a reduction of biodiversity, and climatic catastrophes. Society will depend on life sciences to contribute significantly to solving these problems and alleviating many of the related concerns. Can biotechnologies answer this calling? This constitutes the great challenge of the 21st century. To address this challenge we must accurately assess our current knowledge in order to define what we do not know. For example, researchers tend to focus on the microbial world and on the astonishing diversity of many aspects which remain poorly understood. To take with serious the fundamental question of this, it is to open the way with a number of new applications in several sectors of biotechnologies. A new bioindustry is being created right under our eyes whose potential is immense, and its foundation is what is now called “white biotechnology”, and which uses microbes and enzymes as agents of production. Will this new bioindustry usher us into the age of sustainable development? Can “biofuels” and “bioproducts” of all kinds help save the environment and contribute to a safer future for the planet? In order to accomplish this, the new industry must be economically attractive. But what are the conditions of profitability? The key to success need not, however, be purely economic. There must also be significant support from the society in favour of these technologies. How can we assess today, for the benefit of tomorrow, the interests of the consumer,

* Professor at the University of Paris 7,
General Delegate of the Biovision/Academy of Science Foundation.

the scientific community and industry? Neither can we ignore the question of intellectual property and patents, which must be posed in a transparent and ethically sound manner.

Author Biography

Kenneth N. Timmis



*Professor and Head of Division of Microbiology,
National Research Centre for Biotechnology, Berlin, Germany*

Professor Kenneth N. Timmis studied microbiology at the University of Bristol and undertook postdoctoral training at Yale and Stanford Medical School, during which he was funded by a Helen Hay Whitney Foundation Postdoctoral Fellowship. He was subsequently appointed Group Leader at the Max Planck Institute for Molecular Genetics in Berlin in 1976, Professor of Biochemistry in the Department of Medical Biochemistry at the University of Geneva Medical Centre in 1981, Director of the Division of Microbiology at the German Research Centre for Biotechnology and Professor of Microbiology at the Technical University Braunschweig in 1988. Since 1999, he also holds a part-time appointment as Professor of Microbiology at the University of Essex.

He has published about 400 papers in leading international journals, has been elected to Membership of the European Molecular Biology Organization and the American Academy of Microbiology, and is one of a handful of researchers from Germany and the U.K. that are in the top 100 ISI "Highly Cited Scientists" in the field of Microbiology. In 2001, he was awarded the Erwin Schroedinger Prize for development of the first biotechnological process for the removal of mercury from industrial waste streams. He was the founder and first chairman of the European Organization for Environmental Research, and is the Founding Editor of *Environmental Microbiology* and Editor-in-Chief of *Current Opinion in Biotechnology*.

1

The Challenges for Biotechnology Posed by Human-driven Changes

Kenneth N. Timmis

1.1

Introduction

This chapter explores some of the issues that represent the major challenges in the biotechnology business and that are going to drive future development. We have heard a lot about population growth and megacities, but rather less about the aging population, which will be an enormous challenge in the future with sedentary lifestyles, obesity, diabetes and all of the associated healthcare costs. We also have unsustainable practices which include agriculture, but also industrialization. Industrialization in response to this population growth, which depletes natural resources of course, generates pollution and environmental degradation. Also, interconnected with all of that is global warming and extreme weather patterns that often cause flooding. All of these are exacerbating depletion of natural resources, causing pollution and environmental degradation and leading to epidemics, the emergence of new diseases and, what everyone is very nervous about at the moment, the spread of antibiotic resistance. If one considers antibiotic resistance as a topic which is intimately connected with antibiotic use in intensive agriculture, but also in terms of clinical use, in hospitals, then one can see immediately the link with the aging population, which is a population that is increasing, spending more time in hospitals and being exposed to those pathogens.

1.2

Rising to the Challenge

We need urgent action at different levels and ways to solve or mitigate against the tractable problems. I emphasize the word tractable: many of these problems are not tractable, but some of them are, and those are the ones that we have to

address. These actions have to take place at the level of the political debate, economics, social aspects and technical issues. New technologies have to address the primary issues of improving the human condition, increasing productivity and fulfilling sustainability criteria. Biotechnology is unique in terms of technology, in that it has applications in so many spheres: in medicine, agriculture and environmental repair, but also in terms of sustainability, energy and renewable resources. There is a great deal of excitement over fuel cells at the moment, and also there are bioprocesses that consume less energy. We all know about washing machines and how much energy they consume, and therefore there is an effort to find detergents and enzymes that work at much lower temperatures so that the washing machines can run at lower temperatures. Hence we need catalysts which work optimally at lower temperatures.

1.3

Biodiversity

One should also consider the area of the biochemical cleaning of dirty fossil fuels, those which have high sulfur contents. We can use microbiology to remove the sulfur, and this is, of course, “white biotechnology”. However, we should not forget topics such as mining, biomining and the exploitation of microbes to leach metals from mineral ores as an alternative to thermal removal of metals from ores with the resulting release of sulfur dioxide and other sulfur gases into the atmosphere. Further, there are new materials such as biodegradable materials. One of the drivers that we are facing at the moment is technology explosion: we have experienced technology explosion over the last two decades or so and it is not slowing down. This technology explosion is generating a tremendous need for new materials and processes and some of those can come from biotechnology. So, where will the new applications come from? It is likely that it will come from biodiversity, the greatest source of which is to be found in the microbial world. The tree of life shown in Figure 1.1 is a phylogenetic tree, so the sizes of the elements represent phylogenetic diversity. One can see that the Bacteria, one kingdom of the tree of life, occupy an enormous space, a diversity space, as do the Archaea. The Eukaryotes, which have complex cells, the kingdom to which we belong, occupy roughly one-third of the tree. In fact, in the Eukaryote kingdom, most of the diversity space is also occupied by microbial organisms. Hence this is an enormous phylogenetic diversity when we are looking at microbes and this is what we imagine will fuel new biotechnological developments.

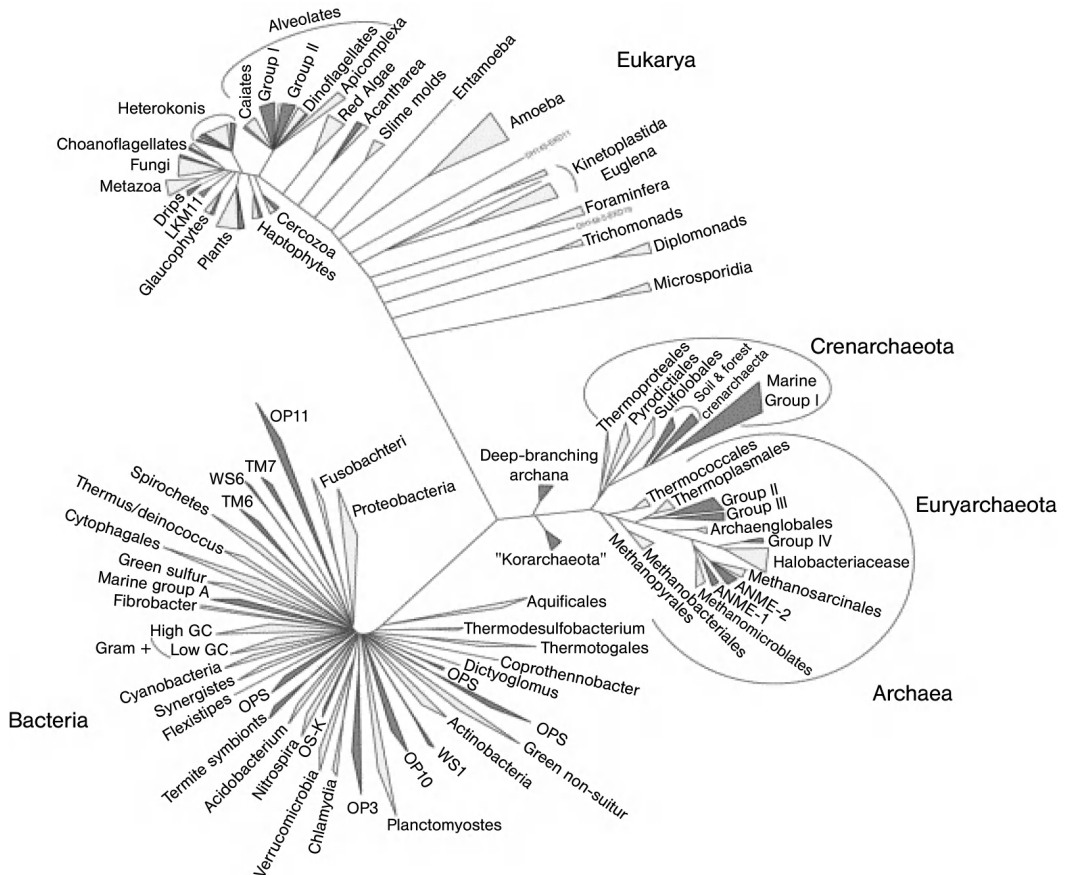


Figure 1.1 The phylogenetic “tree of life” showing the three kingdoms of Bacteria, Archaea and Eukarya.

1.4

Biodiversity – A Hidden Treasure?

One problem is that whereas most higher organisms, things that one can see have been gathered already and described and studied to some extent, microbes by definition are so small they cannot be seen with the naked eye. Hence the only way in which we can actually study them is to cultivate them in the laboratory to amplify them until they become something that we can see, so that there is enough biomass that we can work with. The big problem is that more than 90% of the microbial world cannot currently be cultivated, so we are not able to amplify it. This therefore represents a treasure chest for future biotechnology, but at the moment it is hidden. So, how do we unlock the

value of microbial diversity? The first thing we have to do is, of course, to try harder to cultivate, and many groups are attacking this absolutely essential task. It is very rewarding when it is successful, but it is inefficient, it is mostly unsuccessful and it is extremely slow.

1.5

Metagenomics

The second approach is to harvest the genetic resources of the microbial biosphere, and to do that in an organism which can be grown in laboratory and will act as a surrogate. This is called metagenomics. Craig Venter discusses metagenomics in Chapter 9 so it will not be considered in detail here, but is fast, but is very complete, and it is very biased, but is very powerful. In this approach, one samples some of the material of interest, such as garden soil or the intestine, then extracting the DNA from that sample one generates a library in an organism that can be cultivated, screen it for an activity or sequence it, then characterize it and, if it is going to be applied, one would optimize it and then apply it (Figure 1.2).

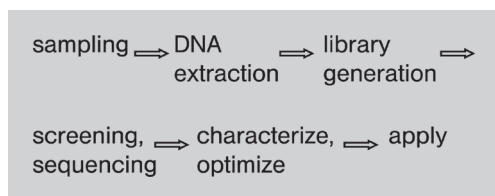


Figure 1.2 The strategy for unlocking the value of microbial diversity.

1.6

New Metabolic Diversity

Together these two approaches are providing new important microbial diversity, new processes and new insights into biological mechanisms. Hence a question that can be posed and answer whether the unknown microbial diversity really reflects new metabolic diversity. Are there new biomolecules and new mechanisms out there? Two examples will be given: one is concerned with biocatalysis, but also with energy conservation, and the other one with white biotechnology, considering how diverse the enzymes out there are that we can perhaps use for green chemistry.

1.6.1

Biocatalysis

In terms of energy conservation, using less energy and operating at lower temperatures means using cold-adapted enzymes. In addition to the obvious advantage of cold-adapted enzymes, there are some others. In some cases, we have high enantioselectivities at low temperatures and, of course, if we want to use them to degrade pollutants by remediation in cold environments, then we need enzymes that will work well in cold environments. Where does one go looking for cold-adapted enzymes? An obvious place is cold climates. We therefore went to Antarctica and isolated an organism, *Oleispira*, which is a member of a completely new class of microorganisms called the hydrocarbonoclastic bacteria (HCB) (Figure 1.3). They are marine organisms that specialize in crude oil degradation and are very important in marine ecosystems for degrading oil spills. We therefore thought that we would look at this organism for interesting cold-adapted enzymes and we chose an esterase as a model system. Figure 1.4 shows part of a library out on a plate; all of the light specks on the plate are phage plaques. The positive plaques were purified and the genes were sub-cloned and hyperexpressed. Purified esterase proteins were obtained but unfortunately the esterase that resulted was practically inactive. One of the reasons for this might be misfolding of the protein and if one thinks of misfolding of proteins, one thinks of proteins which tend to fold other proteins, the so-called chaperones. We therefore carried out a 2-D gel of the proteins made by *Oleispira* at two temperatures, 20 and 4 °C (Figure 1.5).

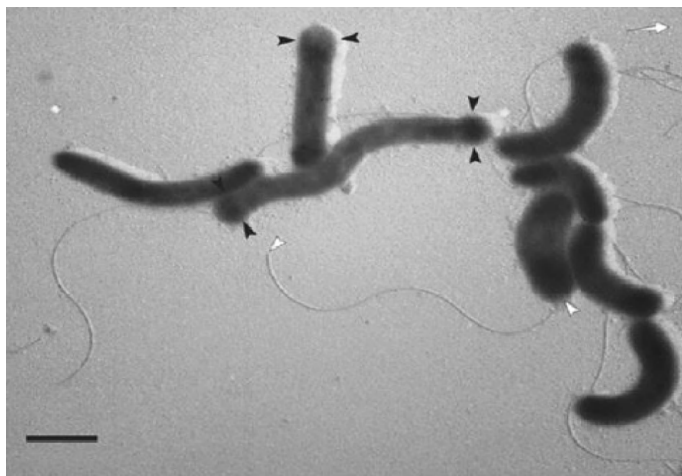


Figure 1.3 *Oleispira antarctica*, a psychrophilic hydrocarbonoclastic bacterium isolated from a crude oil enrichment of Antarctic seawater. (Source: M. Yakimov et al., Int J. Syst. Evol. Microbiol. 53, 779–785, 2003).

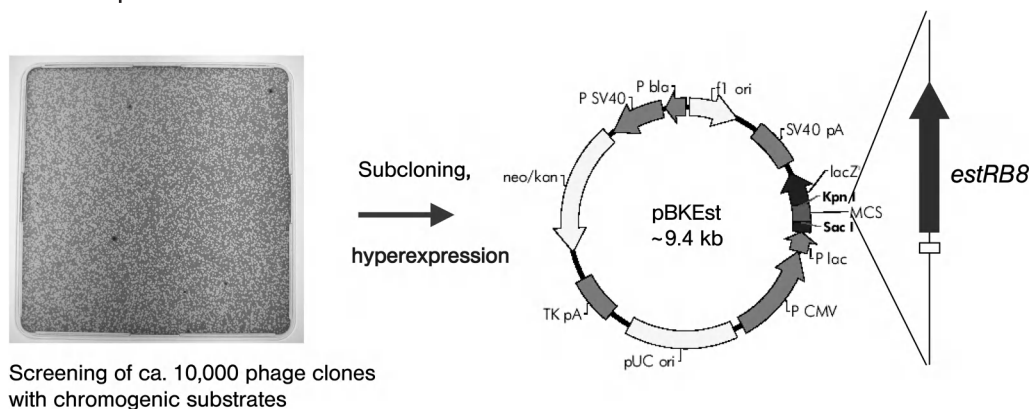


Figure 1.4 Cloning an esterase from an expression library of the *O. antarctica* genome.

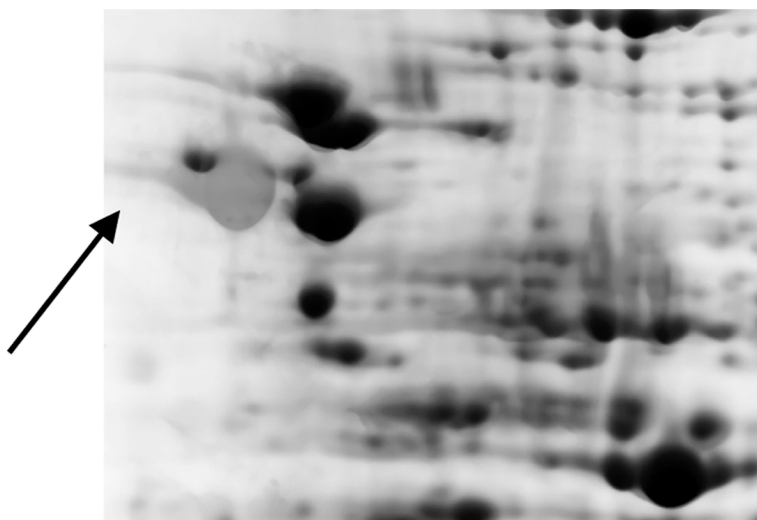


Figure 1.5 Expression of a novel chaperone protein is induced in *O. antarctica* by growth at low temperatures. The figure shows an overlay of 2D protein gels from bacteria grown at 4 and 20 °C. A major new protein is contained in bacteria grown at 4 °C (arrow).

It can be seen that one protein is massively overexpressed by *Oleispira* at 4 °C; this was sequenced and analyzed and it was revealed to be the homolog of the *Escherichia coli* GroEL protein, and this is the major chaperone of *E. coli*.

This suggested that chaperones may be very important for growth at low temperatures and for expression of cold-adapted enzymes at low temperatures, so we went back to the library and looked for those clones which would have the chaperones from *Oleispira*, and obtained some interesting results.

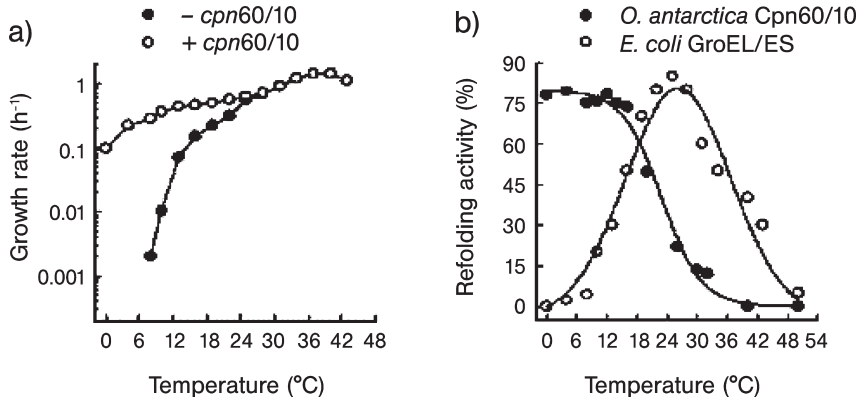


Figure 1.6 (a) Expression of the cold-adapted chaperonin Cpn60/10 from *O. antarctica* lowers the minimum growth temperature in *E. coli* from 7.5 to below 0 °C and substantially improves growth at temperatures below 20 °C. (b) The temperature optimum for the refolding activity of the indigenous *E. coli* chaperonin and the cold-adapted chaperonin from *O. Antarctica*.

Figure 1.6 shows the *in vitro* refolding activity of the *E. coli* GroEL chaperones and it can be seen that the optimum is around 25–27 °C. There is almost no activity below 10 °C, which is the optimum of the *Oleispira* chaperones, and it can be seen that the latter is optimally active at very low temperatures. The plot of growth of *E. coli* against temperature shows that the growth *E. coli* slows below 25 °C and it stops growing at 7.5 °C. However, *E. coli* with the *Oleispira* chaperone grows well at very low temperatures, such as 0 °C, and in fact equations can be applied to calculate what the minimum theoretical growth temperature of *E. coli* is, and it turns out to be –13 °C. Therefore, we changed the lower growth temperature of *E. coli* with the introduction of this one function from 7.5 °C to below 0 °C. Figure 1.7 shows the activities of the esterase in *E. coli* grown at 37 °C and in *E. coli* that has the chaperone grown at 4 °C. The different columns are different substrates for the esterase. The scale is logarithmic, so we see 200-fold higher activities when we prepare this esterase in *E. coli* that has the chaperone.

Let us consider the significance of the above. The first point is that if one uses *E. coli* and would like to isolate new diversity and particularly would like to focus on cold-adapted enzymes, then this will not be successful. Hence *E. coli* and perhaps other hosts fail to capture this segment of functional diversity. However, the *E. coli* just described, which carries the chaperones of *Oleispira*, constitutes a new cell factory for creating genomic libraries or metagenomic libraries of psychrophilic microbes and for expressing those proteins, and it may also be used for expressing other problematic proteins that have nothing to do with cold adaptation but have to do with other folding problems. More broadly, it has implications for biogeography. The bio-

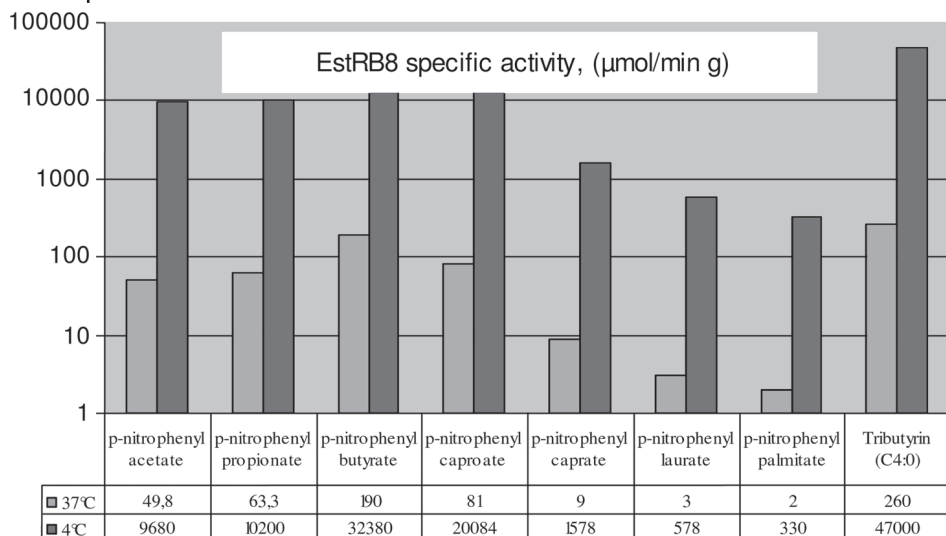


Figure 1.7 Activity of cold-adapted esterase RB8 in *E. coli* expressing the Cpn60/10 chaperonin at 4 °C versus the same activity in wild type *E. coli* at 37 °C.

geography of an organism, that is, where it can live and reproduce, is the key element of its identity and it reflects its survival windows, temperature or pH or something else which are determined by its inherent cellular and physiological characteristics. The mechanisms that underlie such survival windows that determine biogeography are still largely unknown. We now know that in *E. coli* it is the GroEL chaperones which determine the lower temperature window of growth by failing at 7.5 °C. We can again ask the question posed at the beginning: does this new diversity reflect really new mechanisms and proteins? This appears to be one example where it does.

1.6.2

Biodeep Project

The second strategy is more classical, and the example is the so-called Biodeep Project. This was a European project supported by the EC to explore deep hypersaline and anoxic basins of the Mediterranean Sea (Figure 1.8). There are three such basins that are clustered together just west of Crete and a further one closer to the coast of Africa. These basins hold hypersaline dense brine 3–4 km below the surface of the sea, they do not mix with the overlying water column and they are considered to have been isolated for thousands of years, so the question here was whether there is new life. The aim was to prospect these basins and to look at the functional diversity.

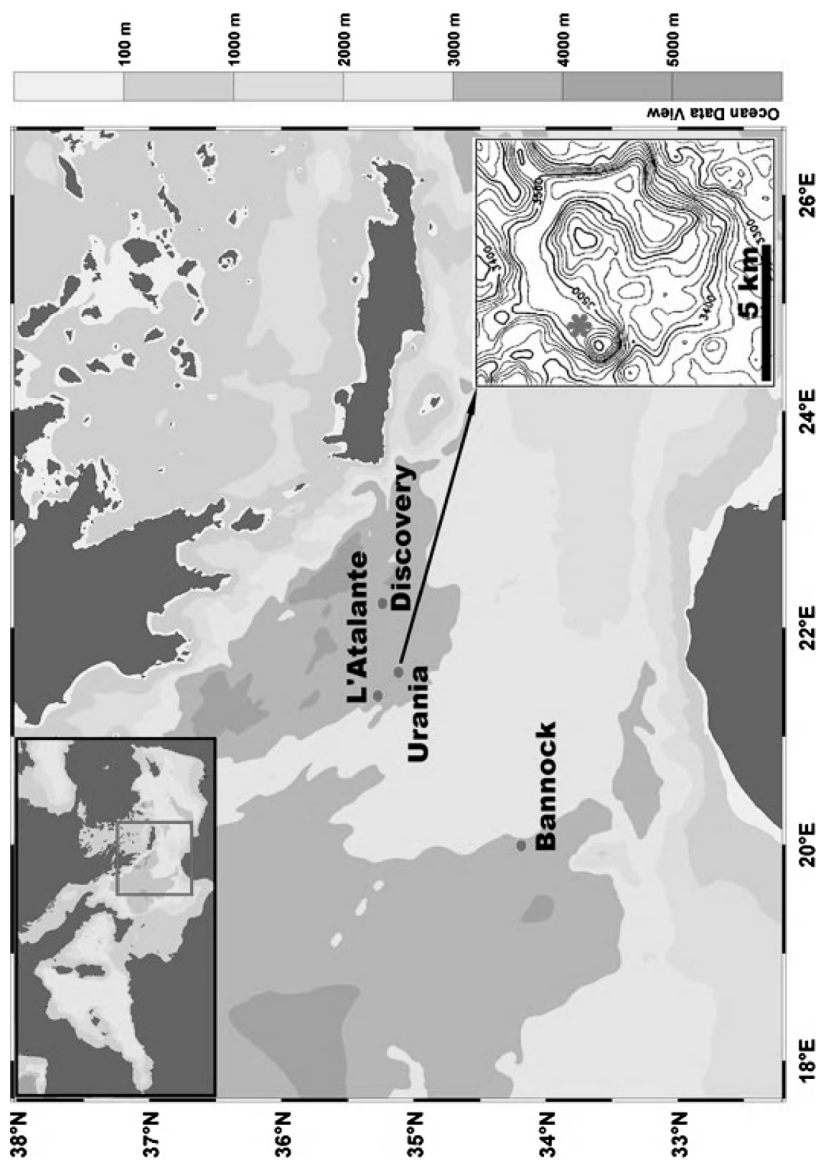


Figure 1.8 Hypersaline anoxic basins in the Mediterranean Sea explored during the Biodeep Project.

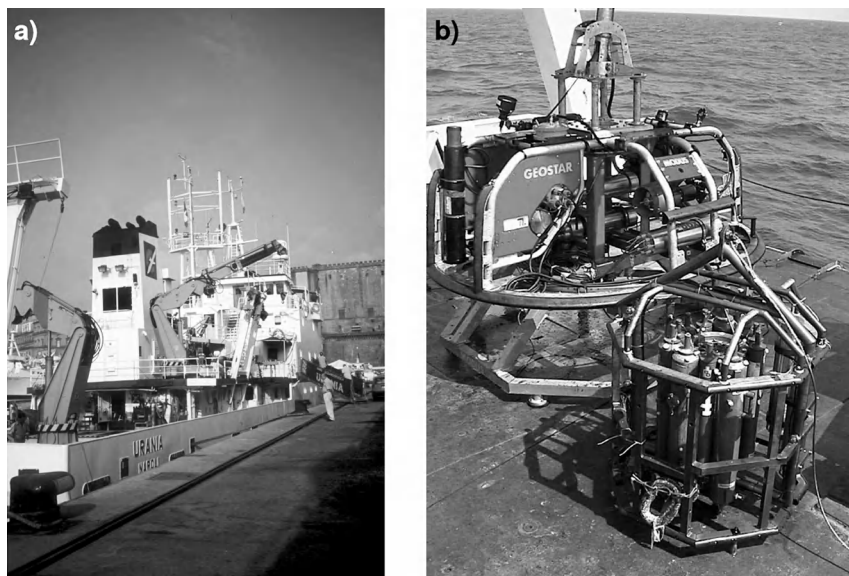


Figure 1.9 (a) The oceanic research vessel Urania.
(b) The sampling equipment used to collect water and seafloor samples from the oceanic basins.

Figure 1.9a shows the Italian research vessel Urania, which actually discovered the Urania basin discussed here, and Figure 1.9b shows the sampling equipment that was used – fairly complex with all kinds of monitors. It needed a cable to lower it down to 4 km and of course a certain amount of instrumentation was required to monitor what was happening 4 km down with the sampling gear. The box shown in Figure 1.10a takes sediment samples and the sample in Figure 1.10b generated the same kind of excitement that bringing home rocks from Jupiter would bring for astro-biologists!

Just a brief description will be given of one small part of the results of this project. What is discussed here is the interface, not the brine itself and not the overlying sea water, but the interface, where there are extremely sharp gradients of oxygen and sodium chloride, going from normal oxygen down to anoxic over a distance of about 1 m and with sodium chloride going from about 0.1 to 5 M over the same distance. There is a pressure at that depth of 40 MPa. We extracted DNA, made libraries and screened for esterases. Table 1.1 gives the properties of the five esterases that we looked at. Two were of particular interest, having salt optima of up to 4 M. They do not work effectively under normal conditions and are much better under high salt conditions. Further, they work best at very high pressures, 20–30 MPa, and are very stable at 40 MPa, and they are resistant to polar solvents. It is a very unusual characteristic of an enzyme to be resistant to polar solvents, but this

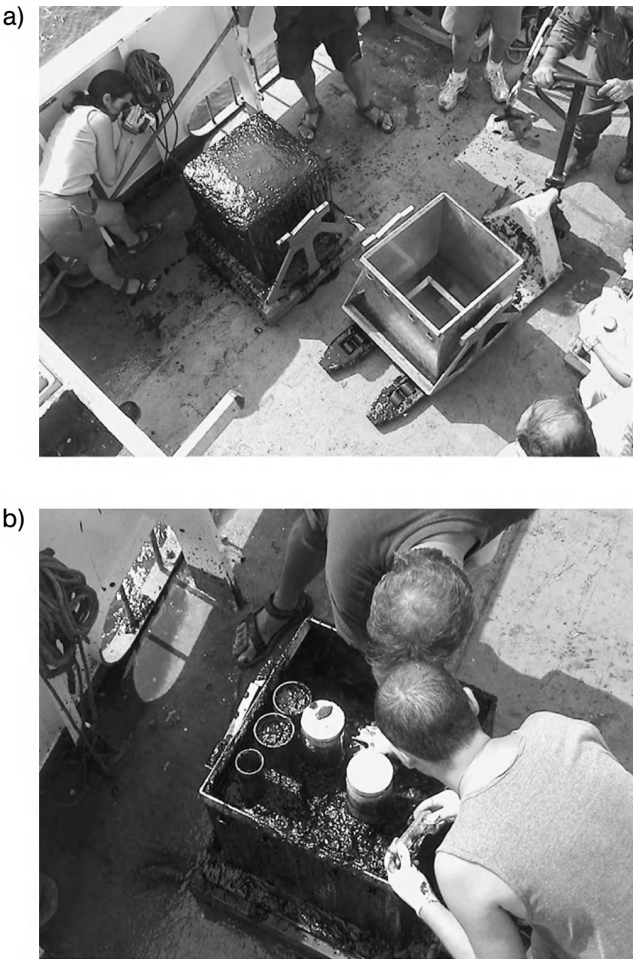


Figure 1.10 (a) Box containing sediment samples.
(b) The first sediment samples recovered from the seafloor of the basins.

Table 1.1 Properties of esterases expressed from DNA found at the interface between normal and hypersaline seawater.

<i>Esterase</i>	<i>[Na⁺/K⁺] opt. (M)</i>	<i>Pressure opt. (MPa)</i>	<i>Pressure stability (MPa)</i>	<i>Polar solvents^{a)}</i>	<i>Reducing agents^{a)}</i>
0.02	< 0.025	0	5	S	S
0.03	2–4	30	40	R	R
0.04	3.5	20	40	R	S
0.05	0.05	0	5	S	S
Oil 2	3.5	0	5	S	S

^{a)} R, resistance; S, susceptibility.

is of industrial interest and one of them at least is highly resistant to reducing agents and reducing agents, in general, destroy esterases.

These two enzymes, O16 and the O21, have no homology with any other esterase in the databases and they are bifunctional, with carboxylesterase and acyl CoA thioesterase activities. Could they be interesting industrially? The O16 enzyme hydrolyzed solketal acetate, a synthon used in the synthesis of pharmaceuticals, at rates and with enantiomeric ratios that significantly exceed published values. In a non-denaturing polyacrylamide gel, the O16 enzyme has a monomeric structure and a size of about 100 000 Da. When dithiothreitol is added it splits into two chains and each of these chains has an esterase activity. One chain has the carboxylesterase activity and the other the thioesterase activity. If salt is added a trimer is obtained with a molecular weight of 300 000 Da.

To summarize a lot of work, this enzyme is a bifunctional enzyme and has two activities. There are three catalytic sites; it has a single site for the thioesterase and an overlapping multicatalytic site for the carboxylase activity. Low redox separates the domains, and in that event both of these activities double. High pressure induces trimerization and again the activities double, and high salt induces trimerization and the activities increase 200-fold. If one combines these conditions then one obtains the conditions that would have been present in the brine, trimerization occurs and the activity increases are all additive. Hence this enzyme is very novel, it has an adaptive tertiary–quaternary structure that changes according to the physical and chemical conditions in which the enzymes finds itself and it assures functionality along the very steep physicochemical gradients that characterize this interface. It has very high enzymatic activities and unusual tolerance to polar solvents and reducing agents that make it interesting for application.

If the O16 enzymes serves as a proxy for other enzymes and other metabolic activities in these brines, then considerable new microbial diversity and novel biological activities or mechanisms may be awaiting discovery.

1.7

Conclusion

Considerable evidence that the vast and unexplored microbial diversity harbors novel metabolic activities is available and accessing this diversity will yield knowledge about new biological processes, but also new insights into known biological processes are emphasized. The study of the *Oleispira* chaperones has really given new insights into how they work and how they work differently from the classical chaperones, and also how the classical chaperones may work. There are also new biotechnological applications to expect and we will have also improvements in existing applications.

This chapter started out with urgent needs of the 21st century that require biotech solutions, and now ends with emphasizing urgent needs, i.e. research now needs to push this science forward, one of the tasks clearly being to harvest and express and exploit the global microbial genome.

We have to prioritize environmental research. Environmental research has been very much neglected over the last decade and this has to be corrected, and we also have to legislate for sustainable practices. The regulatory framework needs to be improved and if we can legislate for more sustainable practices, then this will accelerate progress and will promote the implementation of white biotechnology, reduction of pollution and better environmental repair.

Author Biography

Martin Godbout



President and CEO, Genome Canada

Dr. Martin Godbout holds a B. Sc. in biochemistry (1979) and a Ph. D. in physiology and molecular endocrinology from Laval University. From 1985 to 1990, he received a postdoctoral fellowship from the Medical Research Council (MRC) of Canada and went to San Diego, California, where he was trained in Neuromolecular Biology, at The Scripps Research Institute.

In 1991, Martin Godbout came back to Laval University as an Assistant Professor at the Department of Psychiatry at the Faculty of Medicine. The same year, the Quebec Foundation for Mental Disorder awarded him the Grand Prix Recherche for his previous works on Alzheimer's disease. From December 1993 to April 1994, he was Assistant Managing Director responsible for biopharmaceutical industry relations at the Research Centre of Centre Hospitalier de l'Université Laval (CHUL). In 1994, l'Université Laval awarded him of the «Prix Summa» from the Faculty of Science and Engineering, and the same year, he founded BioContact Québec, an international biopharmaceutical partnership symposium.

From May 1994 to May 1997, Martin Godbout was named President and General Manager of Société Innovatech Québec, a \$60 million technology investment fund. From May 1st 1997, he was the Senior Vice-President of BioCapital, a Canadian venture capital firm specializing in seed-to-mezzanine stage private financing of companies demonstrating strong potential in the healthcare and biotechnology sectors. Since April 1st 2000, he is the President & CEO of Genome Canada, a not-for-profit corporation dedicated to investing and implementing a national strategy in genomics and proteomics research in Canada.

Martin Godbout is a member of the board of directors of several Canadian biopharmaceutical companies, foundations and scientific Canadian organiza-

tions such as MethylGene, Confab Laboratories, BDI, Genome Canada, the Biotechnology Human Resource Council of Canada (BHRC), Société Innovatech du Grand Montréal and BioContact Québec. Since October 1996, he is a member of the Board of the "Conseil de la Science et de la Technologie du Québec". He has authored or co-authored more than 60 publications and abstracts, and has been invited as speaker at numerous scientific and financial conferences.

2

Social Acceptance of New Bioprocesses

Martin Godbout

2.1

Introduction

As can be deduced from Chapter 1, the potential for industrial biotechnology is truly breathtaking. The example that Kenneth Timmis presented on *Escherichia coli*, the chaperone and the esterase speaks for itself.

Biomanufacturing is transforming many of the world's industrial operations, reducing or even replacing the use of fossil energy and hydrocarbon-based material with renewable plant-based resources, using naturally occurring microbes to produce more cost-effective, environmentally friendly materials for textiles, fuels, chemicals, pollution prevention and even human pharmaceuticals. This "third wave" in the biotech revolution is opening doors and providing tools that were unimaginable 10 years ago.

Increasingly, industrial biotechnology is becoming the point of convergence for transgenic plants, systems biology, chemistry, nanobiotechnology, etc. – the intersection for so much of what biotechnology has already brought and a signpost indicating that all this is just a beginning.

Genomics will play a key role in industrial biotechnology by producing better crops, enhancing the refining of carbohydrates, converting those carbohydrates into new products and developing new, more effective, microbial strains.

In Chapter 3, Alfred Hackenberger discusses some of the most promising applications of industrial biotechnology and we will get a fuller sense of what the future might hold for this new frontier of biotechnology.

2.2

Social Acceptance of New Bioprocesses

This chapter focuses first on the social acceptance of these new bioprocesses and the challenge that those in the scientific community face and the opportunities that exist.

Certainly, the engagement of society at large is something that Genome Canada has been very conscious of. It is why we have integrated issues such as ethics, the environment, social concerns and legal questions into every research project we are funding and why we have placed such an emphasis on public education and outreach. Finally, some lessons that might be applicable to industrial biotechnology are outlined.

There is simply no doubt that we are living in one of the most exciting periods in the history of science, a time when human creativity is multiplying exponentially, permitting quantum changes to occur, each new breakthrough holding with itself the DNA of another revolution. Nowhere is that revolution moving faster or affecting society more than in biotechnology and, within that sphere, few areas hold as much promise as industrial biotechnology. As scientists, we would like to believe that we will shape its future, define its course and establish its priorities, but we would be deadly wrong.

The reality is that decisions about what priority to pursue or what potential will be realized are ones that will ultimately be decided by society at large and therein lies the problem: while the potential of biotechnology is so profound and its application so universal that all need to be informed, it is a discipline filled with impediments to understanding: specialized vocabulary, complex concepts and an assumption of a working knowledge of science, chemistry, microbiology and a host of other subjects. Such a working knowledge the vast majority of those in our societies simply do not have.

2.3

The Challenge

Here is the dilemma all are facing. We have one of the most important and profound scientific revolutions in history, a revolution that will touch every member of our society and yet informed participation in that revolution is hampered by obscure concepts and technological jargon. And, when on the top of that is layered the very real and understandable ethical and moral concerns that biotechnology raises, one begins to get the sense of the challenge facing scientists. At Genome Canada we have seen this not so much as a reason to despair but as an opportunity to inform, to make the complicated comprehensible, to simplify without being simplistic and to provide society at large with information that is both accurate and understandable. Indeed,

as already noted, we have seen public education and outreach as key parts of our mandate, because we believe that the best way to deal with society's concerns is to acknowledge them honestly, to discuss them frankly and to explain them clearly. If we have learned anything from the debates over GMOs in Europe and elsewhere around the world, it is that the public must be engaged so that these issues are resolved with them, not imposed on them. To borrow the slogan of a well-known Canadian company, "an educated consumer is the best customer". That begins with the very frank acknowledgement that biotechnology, for all its wonders, also brings worries. People are not sure where all of this is headed and new technologies are raising issues we have never had to deal with before, both ethical issues and moral issues.

2.4 Solutions

It is important to recognize and to understand these concerns. Even more important, we need to address them, ahead and up front. That is not just a good strategy, it is the right strategy, it is the honest strategy. And sometimes that means admitting that we do not have all the answers, that perhaps science is not the best place to find them, because the truth is that although science can provide precise information, it cannot provide ethical truths. It can reveal new insights into our bodies and our world, but it cannot provide the wisdom for dealing with those insights. It can, in short, tell us what can be done, but not necessarily what ought to be done. For that, we need the contribution of those who are experts in other fields, ethics, environment, economics, lawyers, and at Genome Canada we felt that it was important to bring these various disciplines together from the very beginning. Not as an add-on or as an afterthought, but as an integral part of all the projects we are financing. This is exactly what has been done both internally, by committing funding to the study of these wider social concerns, and externally, through the sponsorship of conferences and public outreach. In fact, we felt that it was so important that we have incorporated ethical, environmental, social and legal issues into every research project funded in addition to funding separate projects devoted especially to these issues.

2.5 Examples

Some examples are given here. One of our projects on the genome of the potato is focused on identifying genes responsible for potato health, such as resistance to pests and potato quality. This is a very significant project because

the potato is one of the four most widely grown crops in the world, consumed by more than 1 billion people on a daily basis, but there are also important intellectual property issues involved in this project, especially what is called the “innocent bystander”. The innocent bystander issue is one of the key controversies over the patenting of higher life forms. In this case, the innocent bystander could be a neighbor of a farmer using a patented seed who has some of these seeds blown into their own field. If that neighbor allows the plant to grow on their property or intentionally harvests and uses the patent seed, will they infringe patent law? What are the rights and responsibility involved here? These are the kind of issues we are studying as part of the sequence of the genome of the potato. We are also funding research independent of these projects related to what we call GEEELS. GEEELS stands for the economic, environmental, ethical and social issues related to genomics. The titles of some of these projects that are currently being funded are:

- Bridging the Emerging Genomics Divide.
- The Rights and Responsibilities of Genomics in Society.
- Democracy, Ethics, Genomics – Consultation, Deliberation and Modeling.

Also, we have sponsored three international symposia on the ethical, environmental, economic, legal and social issues related to genomics. They have brought together hundreds of experts from around the world, experts in fields as diverse as anthropology, sociology, genetics and philosophy. We have also launched a newsletter devoted to these issues to keep Canadian and other scientists up to date on the latest research and development in these areas. We are even involved in bringing about a successful stage play called “The Score”. It will be a television program that will explore some of the ethical issues related to scientific research, mostly dedicated to breast cancer.

In a field as new and controversial as genomics, we believe that it is our responsibility to lead this discussion, not necessarily to provide the answers, for those are still being sought, not to outline a specific course for the journey that is still being charted, but to provide information and present alternatives to the members of our society, so that they can participate in this discussion and help make the difficult decisions that lie ahead for all of us. To further that goal, we have launched an ambitious public outreach and education effort. In that context, we have provided basic information about genomics and proteomics through such traditional means as news releases, speeches and media information kits. These have worked very well, enabling us to provide reliable information to journalists so that they could prepare their story or file their reports on the sound foundation of fact. We have also put a great deal of effort into creating an innovative and informative website. This was very deliberate. At a time when most Canadians use the Internet to do their research, we knew that it was crucial to develop a really effective website, one that not only contains reliable and credible information, but also one which is

easy to navigate, fun to use and interesting to look at for the younger generation. The website has been very well received, with an average of 10 000 visitors per week. We have also put a great deal of emphasis on reaching young people. These are the future scientists, and the future citizens who will live with the consequences of the decisions we are making today. To reach them, where they live, we have sponsored awards at Canada-wide science fairs, recognizing outstanding projects related to the study of DNA and genetic material.

Perhaps the most successful initiative is called the 'G in Genome'. This is a multi-dimensional traveling exhibition that allows visitors to explore genomics at first hand. The 'G in Genome' has traveled the country, visiting local museums, science centers and high schools. We have also created smaller suitcases that are compact enough to go to the smallest towns, the most remote regions, bringing genomics to people's front doors. Around 400 000 Canadian have either visited the exhibition or participated in its various programs and forums. The full exhibition will travel for 3 years before coming to a permanent exhibit in the Canadian Museum of Nature in Ottawa. This has been a real success and we have been very gratified by the public response.

We also know that the key part of any society is the decision-makers. We have established an ongoing dialog with Members of Parliament, providing analysis and information which has contributed to informed policy making. Recently, we held a day-long event in the Parliament buildings which introduced Members of Parliament from all political parties to some of Canada's leading scientists and leading-edge technologies. These are just some of the things we have been doing at Genome Canada in terms of studying the ethical, environmental, social and legal issues incorporating them into our research and communication with the public.

2.6 Conclusion

What lessons might be learned with respect to industrial biotechnology? First, all of us face the same challenge of a lack of basic information among the public. As we move towards commercialization of these new processes, most people will not be familiar with industrial biotechnology, never mind the science behind it. Therefore, we need to commit to engaging the public, providing information about what we know and being honest about what we do not know. In many ways, industrial biotechnology will be easy to sell. After all, its basic premise and promise bring obvious benefits, its feedstock is sugar, not petroleum, its products are renewable, non-polluting and, in most cases, either biodegradable or recyclable. By using plant materials instead of fossil fuels, we will help to preserve this fuel reserve and achieve a real, sustainable

carbon cycle. Moreover, there are a number of factors which are spurring demand and increasing acceptance for industrial biotechnology within society at large. There are consumers who are facing costs for their heating oil, natural gas and fuel for their cars. There are companies looking for more cost-effective, sustainable alternatives to petroleum and chemical-based materials. There are governments which are investing in industrial biotechnology. There is real political unrest, raising concern about the dependence on foreign oil, and there are climate change and new environmental rules aimed at meeting Kyoto commitments. There is, in short, an environment conducive to acceptance of industrial biotechnology. There is critical challenge and it is one we must meet.

Author Biography

Alfred Hackenberger



President, Specialty Chemicals Research Division, BASF AG

Dr. Alfred Hackenberger was born in Reimsbach, Germany, in 1951. From 1970 to 1976, he studied chemistry at the University of the Saarland. He received his PhD from the Institute of Organic Chemistry of the University of the Saarland in 1980.

He joined BASF Aktiengesellschaft in 1981. In 1986 he was Assistant to the President of the Brazil Regional division, São Paulo. In 1991 he was Sales manager ED (Dispersions) in Brazil, BASF S.A., São Paulo. In 1993 he became Head of the Chemicals division in Brazil, BASF S.A., São Paulo. In 1996, he was appointed Head of CZN/C (Marketing Intermediates) at BASF Aktiengesellschaft, and in 1998, Senior Vice President ZHF (Research Fine Chemicals). In 2001, he was named Group Vice President, Regional Business Unit Fine Chemicals Asia Pacific based in Hong Kong. Since 2004, Alfred Hackenberger has been President of the Competence Center Specialty Chemicals Research, BASF Aktiengesellschaft.

3

White Biotechnology: Science, Fiction and Reality

Alfred Hackenberger

3.1

Introduction

This chapter describes how BASF envisions industrial or white biotechnology today and in the future. What is science? What is fiction? What is reality?

Industrial biotechnology, recently renamed white biotechnology, includes all industrial processes for the production of chemical products and enzymes which rely fully or partly on the biological toolbox of nature. White biotechnology processes take place in a contained environment, typically in a bioreactor in a dedicated industrial plant.

3.2

Outline of White Biotechnology

This chapter discusses the potentials, limitations and challenges of white biotechnology, and also the impact of green biotechnology on white biotechnology. Biological methods have a long history of development and application (Figure 3.1). Since ancient times, simple biological processes have been used for the production and processing of food and beverages. Prominent examples are beer and wine, sourdough and yogurt. The development of a fermentative process for the production of butanol and acetone in 1916 by Charles Weizmann marks the beginning of the use of biotechnology in industry. Soon further products such as glutamic acid and vitamin C were also produced via fermentation. Biotechnological processes currently used in industry can be divided into two classes (Table 3.1). In fermentation processes, living microorganisms directly convert renewable raw materials such as sugar, starch and vegetable oils into complex organic molecules. Biocatalysis, also called biotransformation, describes the use of isolated enzymes as catalysts in a

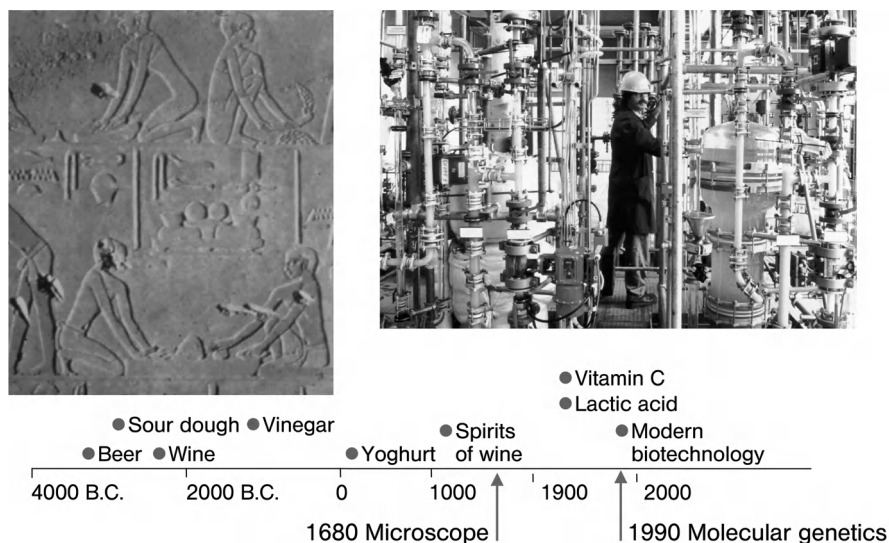


Figure 3.1 Development of white biotechnology.

Table 3.1 The two strategies of white biotechnology.

Strategy	Method	Resource base
Fermentation	Production of compounds by the use of microorganisms	Renewable resources
Biocatalysis	Integration of biotechnology in standard chemical processes	Fossil fuels (oil)

distinct chemical reaction step. These processes were originally developed and optimized by classical breeding of production organisms and process engineering. Substantial progress in biochemistry, genetics, computer science and high-throughput screening has recently generated the new disciplines of enzyme and metabolic engineering. Enzyme engineering uses modern techniques to mimic evolution in the test-tube. Furthermore, it takes advantage of new methods to access biodiversity. As a result, a tremendous amount of novel tailor-made biocatalysts can be generated within a short period of time. Metabolic engineering means the shift from random strain improvement to the rational design of production organisms. The use of genomics and other “-omics” technologies results in a better understanding of metabolic pathways. Subsequently, these are optimized using gene technology. Consequently, the development times of biotechnological processes are significantly shortened. In addition, new products, production processes and solutions will be accessible within biotechnology in the future. This opens up the opportunity

for white biotechnology to increase the use of renewable resources and the chemical value chains.

Today, these chains are almost exclusively based on fossil raw materials, mainly oil. Because of those perspectives and the recently increasing oil prices, a heated discussion in industry, politics, the scientific community and society is in progress to consider if renewable resources can be used for the production of biochemicals. Are we therefore close to a technical revolution in a chemical industry? The answer seems to be a clear “no”. Without doubt, white biotechnology offers a broad array of chances in the chemical industry, but we need to be realistic in order to harness the relevant opportunities. This means that we must also be aware of the limitations.

3.3

Relevance of White Biotechnology for the Chemical Industry

In 2001, the worldwide turnover of biotech chemicals was in the range of €33.5 billion. This is definitively an impressive amount, but actually it represents a market share of only 2% of the total chemical market, not including pharmaceuticals. The most important product is bioethanol, which that accounts for half of the above amount. One-quarter of all sales are made with complex intermediates produced by superior biotechnological methods.

3.4

Achievements of White Biotechnology

Let us consider what biotechnology can really achieve. White biotechnology offers various chances, predominantly the following:

- reduction of reaction steps in production,
- reduced use of raw materials including the option for the use of renewable raw materials,
- savings in energy due to the reduction in reaction steps, workup procedures and reaction temperature,
- reduction of emissions,
- reduction of production costs,
- opportunities for the development of new products.

To demonstrate these achievements, let us consider the example of the fermentative production of a fine chemical, the synthesis of vitamin B₂. Until 1990, vitamin B₂ was produced in a complex organic process including eight individual chemical reaction steps. After years of intensive research, BASF managed to shift this chemical process to a one-step fermentation process

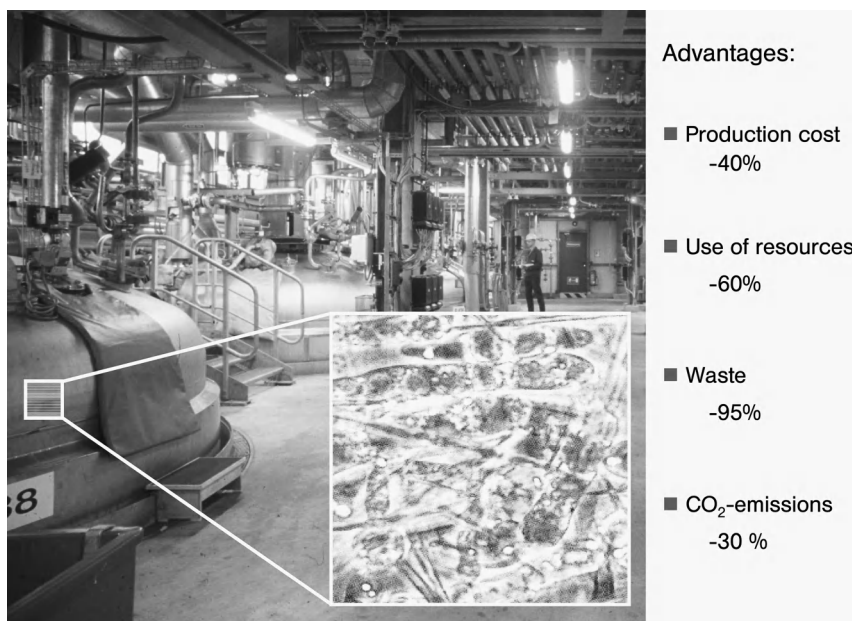


Figure 3.2 Production of vitamin B₂ by fermentation.

based on soybean oil. Overall, this change in production offered several significant advantages that are shown in Figure 3.2. Today, more than 85% of the worldwide vitamin B₂ production is done by fermentation.

A second example of superior biotechnological methods is the production of chiral amines with biocatalysis (Figure 3.3). Here the catalyst is an immobilized enzyme. A racemic mixture of an amine is treated with an ester in the presence of an immobilized lipase. Only the *R*-enantiomer reacts with the enzyme to give the amide; the *S*-enantiomer remains unchanged. Owing to the immobilization of the enzyme, the process can be run continuously and the workup procedures follow standard techniques, in this example distillation. Both products can be used as chiral building blocks for pharmaceuticals, agricultural products or in the food and feed industry. The photograph in Figure 3.3 of the plant where this process is run shows that biocatalysis involves large-scale technical chemistry. Using different types of enzymes, a broad portfolio of chiral compounds can be made, such as amines, alcohols, epoxides and hydroxy carboxylates.

The third example shows another possibility of how biotechnology can provide innovative solutions for the needs of customers (Figure 3.4). Pigs and poultry lack specific enzymes to release phosphorus bound to inositol. Therefore, extensive feeding with inorganic phosphorus is crucial for growing these animals. The BASF product Natuphos releases phosphoric acid from

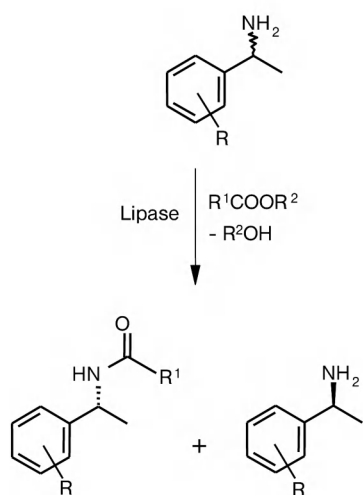


Figure 3.3 Use of enzymes, in this case a lipase, in the production of chiral chemicals. The photograph shows the ChiPro[®] plant at Ludwigshafen, Germany.

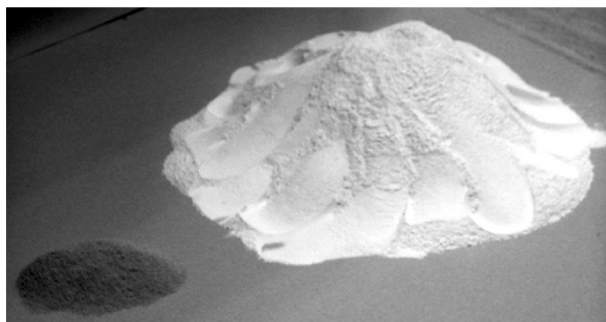
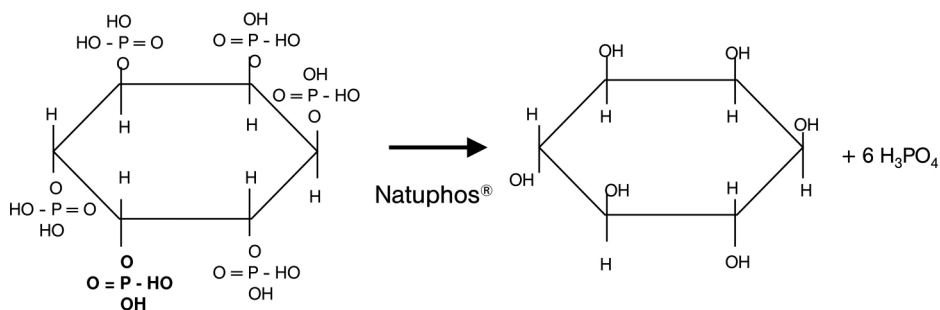


Figure 3.4 Use of enzymes as feed additives. A 100 g amount of the Natuphos enzyme additive replaces 6.4 kg of calcium phosphate in feeding livestock.

inositol hexaphosphate and leads to a 30% reduction of phosphorus excretion, healthier animals, better nutrient uptake and replacement of organic sources of phosphorus.

3.5

Limitations of White Biotechnology

The above examples demonstrate the broad scope of applications that biotechnology already holds today within the portfolio of a chemical company such as BASF, but there are also limitations. Let us consider first the economic challenges. White biotechnology is not a universal miracle cure. First, biotechnological processes are not intrinsically superior to established chemical processes. In each individual case, we have to analyze which process is the best, taking into account costs, consumption of energy and resources and emissions. This is demonstrated by the eco-efficiency analysis of indigo, which is a well-known blue dye for genes. Eco-efficiency analysis as a general tool was developed by BASF for determining and quantifying the sustainability of products and processes. It provides an assessment of the total costs and environmental impact that a product or process creates over its complete life cycle starting with raw material extraction and continuing on to post-use disposal or recycling. Initially, indigo was extracted from plants. The ranking of this process in an eco-efficiency analysis is indicated in the lower left corner of Figure 3.5. At the end of the 19th century, industry managed to establish a chemical route for indigo labeled as granulate in the figure. Finally, a ferment-

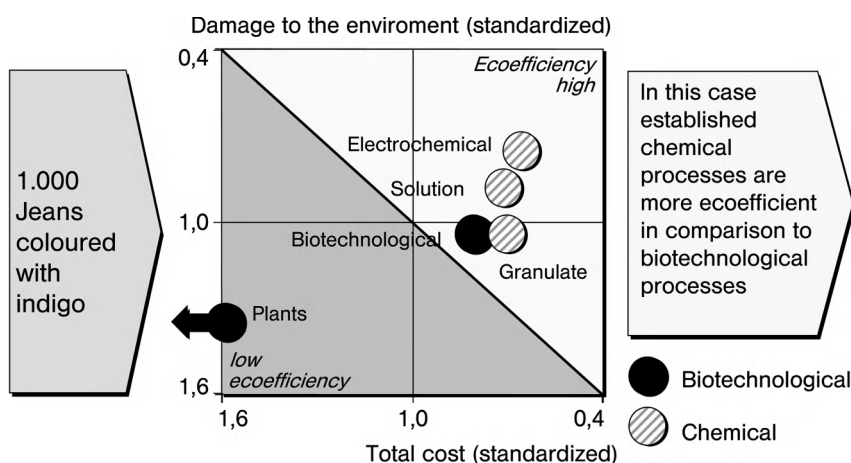


Figure 3.5 Eco-efficiency analysis of indigo production.

The biotechnological production is inferior to production by chemical processes in terms of environmental impact and overall cost.

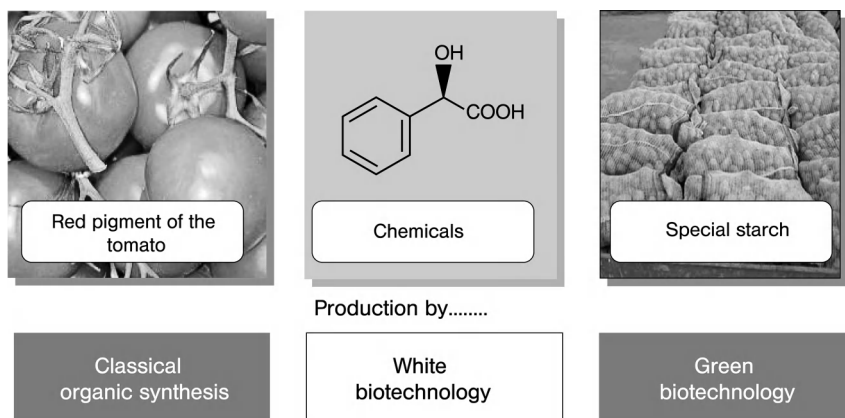


Figure 3.6 White biotechnology as an addition to the synthetic toolbox.

tation route was established by molecular biologists in the 1980s. This eco-efficiency analysis shows that this fermentation process is far superior to the use of plants, but that the chemical processes are superior to biotechnology.

Second, biotechnological processes are not instantly available. Even though many things are theoretically conceivable, we are often a long way away from realization on a technical scale. Often these processes need many years of effort in research and development. In addition, it is time consuming and expensive to switch from a chemical to a biological synthesis. An example is the above-mentioned synthesis of vitamin B₂.

Third, in chemical production, white biotechnology will not be the only tool, but will be definitively one of several. In BASF, we therefore consider white biotechnology as a valuable part of our technical toolbox along with classical chemistry and green biotechnology. The three new products in Figure 3.6, each developed using different technologies, nicely illustrate the strategy. The red pigment of the tomato, lycopene, is made via classical organic synthesis. Complex intermediates such as mandelic acid are produced with white biotechnology. Special starch or raw material for the paper industry will be made by green biotechnology in the near future. In each case, the technology chosen has proven to be superior to all others.

Despite tremendous progress, white biotechnology nevertheless still faces technical limitations. Fermentation still focuses on the production of natural products such as amino acids, vitamins and enzymes. To enter the value chains of the chemical industry, the scope of fermentation processes must be broadened towards the production of unnatural chemicals by design of artificial metabolic pathways. Here sulfur- and halogen-containing molecules and structural polymers will be a tremendous challenge. Even in the field of natural products, there are limitations, namely the production of lipophilic and sulfur-

containing molecules. For instance, the economically important natural products vitamins A and E and also carotenoids and methionine cannot yet be produced on an industrial scale by fermentation. Here all efforts in white biotechnology have failed so far. In this sector, green biotechnology will offer interesting new alternatives, such as expressing lipophilic substances in oil-producing plants.

There is also a challenge regarding the raw materials used so far in fermentation. Currently, industrial fermentations are based on high-value agricultural products such as sugar, starch and vegetable oils. In order to boost significantly the number of white biotechnological applications, processes must be available that give access to cheap biomass. Here we need new enzymes that convert cellulose and other biomass into small molecules that can be taken up by microorganisms. These new production strains, capable of growing on hydrolyzed biomass, also have to be developed. Hence the use of biomass as a fermentation raw material will result in a complex fermentation broth containing much more byproducts than the processes today. Consequently, we need to develop entirely new recovery processes, especially for solid products and products that will be converted by an additional continuous and catalytic reaction step. Also, green biotechnology is expected to make a contribution to the cheapening of renewable raw materials. Plants with higher yields and plants with higher draft and cold resistance will contribute to lower the raw material costs of fermentation. Overall, low raw material costs are an absolute prerequisite to make white biotechnology a valuable tool for the production of bulk chemicals. Whoever is the first to overcome the above limitations will have an outstanding competitive advantage. This requires further cutting-edge basic and industrial research and the strengthening of scientific networks. The close cooperation between chemistry, biology, molecular biology and process engineering involving academia start-ups in industry is indispensable. The recently formed European technological platform for sustainable chemistry with its subgroup white biotechnology is one ideal instrument for that purpose. Therefore, we expect politicians to fund interdisciplinary basic research and research organizations as industry has done for many years.

Another success factor for white biotechnology in Europe is international competitiveness. Whoever wants to encourage the use of white biotechnology should not do it by regulations or quotas that invalidate market mechanisms. Neither the decision as to whether a chemical or biological processes is the right choice, nor the choice between fossil or renewable resources, should be stipulated by legislation.

3.6

Conclusion

Considering the market share of 2% that biotechnology has today in the total chemical market, I do not believe that it will have a market share of 10%, 20% or even more in 2010. However, I envision white biotechnology as one of the strongly growing segments in the chemical industry with growth rates significantly higher than those of the chemical markets. Figure 3.7 shows the current and future main growth areas for white biotechnology. In the next few years, new fermentation processes for the production of fine chemicals will contribute substantially to growth in this sector. Also, intermediates and performance products will be among the growth drivers spurred by recent progress in biocatalysis. Laboratory-scale and a few pilot-scale processes for the production of biopolymers have recently been improved owing to successful research in the previous couple of years, but they still suffer from high production costs. In this field and also in the field of the production of bulk chemicals, much more research effort is required to achieve competitive biotechnological processes. We see interesting concepts in the laboratory and expect major scientific breakthroughs within the next few years. It remains to be seen if and when this will result in significant contributions of white biotechnology to this area.

BASF has integrated sustainable development as one of four key aspects into its corporate strategy. Owing to the advantages of white biotechnology pointed out above, the broad experience gained with running biotech processes and exciting research perspectives, I consider white biotechnology as a tool of growing importance for ensuring sustainability in the chemical industry.

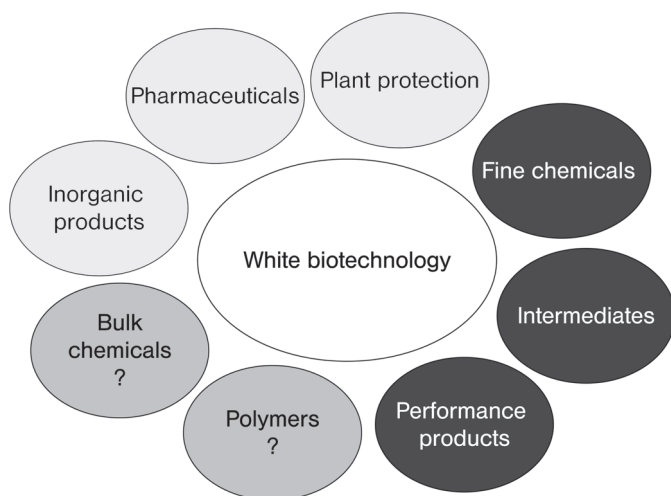


Figure 3.7 The BASF vision of white biotechnology.

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Module II

Climate and Health

Introduction

Dominique Lecourt

It is well established that diseases can be induced by a climatic change. The relation which binds this change to the proliferation of, for example, a certain virus depends in turn on the modification of the ecosystem. Thus a new field of research is taking shape: ecology of infectious diseases. It is impossible to forget the disastrous impact of the heatwave during the summer of 2003 and the devastation it wrought on the elderly in France.

It is increasingly urgent to actively thwart climatic change ascribable to human activity, particularly that arising from industrial production. For this purpose “white biotechnology” provides powerful tools. These technologies have already proven useful through the development and use of industrial enzymes, and their use in producing a variety of products provides a powerful basis for substituting the use of other biotechnological tools for the traditional ones. Are the economic and political decision makers ready for such change? How can we avoid a development time line that is not considered too long by both the industrialists and elected officials? How can we organize a democratic and fair means by which decision-makers can operate using a twenty-five year horizon, whereas today they must operate in the near-term of three to five years.

Author Biography

Terry L. Yates



Vice Provost for Research, University of New Mexico

BS Degree, 1972, Murray State University, Murray, Kentucky; MS Degree, 1975, Texas A&M University, College Station, Texas; Ph. D. Degree, 1978, Texas Tech University, Lubbock, Texas.

Current positions: Vice President for Research & Economic Development, University of New Mexico; Professor of Biology and Pathology, University of New Mexico; and Curator of Genomic Resources, Museum of Southwestern Biology, University of New Mexico. Immediate past positions: Vice-Provost for Research, University of New Mexico; Director Division of Environmental Biology, National Science Foundation; Professor and Chair, Department of Biology, University of New Mexico; Director, Museum of Southwestern Biology, University of New Mexico; Director, Systematic Biology Program; and Head Systematic and Population Biology Cluster, National Science Foundation. Past Chairperson, Systematic Collections Committee and International Relations Committee, American Society of Mammalogists.

Over 120 papers published in refereed outlets; completed 16 Ph. D. and 9 Masters students; Member, Board of Directors and Chairman Board of Trustees, American Society of Mammalogists; Trustee, Southwestern Association of Naturalists; Vice-President, Natural Science Collections Alliance; Member, Board of Directors, Peromyscus Stock Center; Chairman, Board of Trustees, Society of Systematic Biology; Member, Board of Directors, National Lambda-Rail Incorporated; President, Monzano Conservation Foundation; Member, Board of Directors, La Semilla Institute; Member, Executive Board of Directors, Science & Technology Corporation @ UNM; Member, Board of Directors, New Mexico Technology Research Corridor; 1991 recipient, Leopold Conservation Award, The Nature Conservancy; 1995 recipient, Robert L. Packard Outstanding Educator Award, Southwestern Association of Naturalists.

Currently funded research projects on surveillance and monitoring of Hantavirus in natural populations of mammals, Center for Emerging Infectious Diseases, International Center for Infectious Disease Research, Knowledge and Distributed Intelligence, Bioscience Center for Informatics, University DTRA Partnerships, and the Seville Long-Term Ecological Research project.

4

Climate and Health: Predicting the Spread and Risk of Infectious Disease

Terry L. Yates

4.1

Introduction

Using a level 4 virus, hantavirus, as an example, this chapter illustrates what we need to do in order to be able to achieve a level of predictive understanding for zoonotic diseases and hopefully to a point where we are actually able to do forecasting in this area. Hantavirus is a particularly good example because it seems to be heavily driven by climatic factors and also by factors involving human influence. The interaction between those complex phenomena of environmental ecological evolutionary and human factors demonstrated here provides an example of the kinds of complexity that we have to understand.

4.2

Background

In 1993, young and seemingly very healthy people began dying in the southwestern United States, centered in New Mexico, Arizona, Colorado and Utah. Nobody knew why these young people were dying and there was no treatment and no cure at the time. Such events were unknown in the USA and created great concern: to illustrate how panicky even the medical profession got, the notice in Figure 4.1 was put up in the major clinic in Gallup, New Mexico, where this outbreak was centered. Very quickly, we were able to determine with help from CDC and others that the infecting agent was a hantavirus. Hantavirus is common in Europe and Asia, but this one was different in many respects. The molecular evidence suggested that this infecting agent was newly recognized. We knew that the RNA sequences from tissues from different patients were homologous, the viral sequences from rodents were homologous with that of the patients and so it was clear that

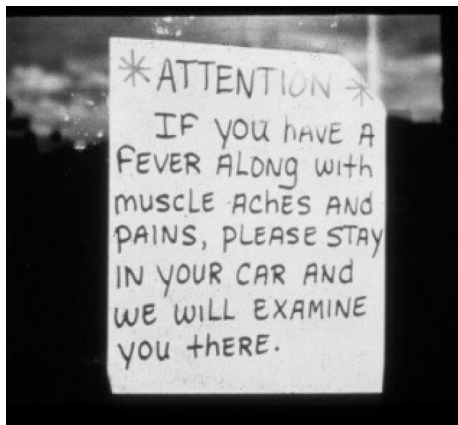


Figure 4.1 Notice posted at the Gallup clinic during the first outbreak of hantavirus in the USA in 1993.

that was the infecting agent and it was new. We compared it with other samples from around the world very quickly to confirm that.

4.3

Hantaviruses

Hantaviruses belong to a family called Bunyaviridae. They are encapsulated RNA viruses. It turned out this new agent caused hantavirus pulmonary syndrome (HPS) in humans. People basically drowned from fluid leakage in the lungs and that is one of the reasons why we missed it because most of the other known forms cause renal syndrome and hemorrhagic results. The mortality rate was and still is in excess of 40%, so this is a bad disease to catch. The primary reservoir was a small rodent, a deer mouse (Figure 4.2). This mouse is in a very common worldwide family of rats and mice that are almost ubiquitous around the globe. If you are a virus and need a host, this mouse is a good one, but it makes it very troublesome for humans.

4.4

Biodiversity

If we want to really model and predict emerging zoonotic diseases, then we at least need to have a baseline and know what is out there. I contend that we understand very little about biological diversity even of the world's most deadly viruses such as this one. In 1993, however, when this new virus was discovered,



Figure 4.2 The deer mouse (*Peromyscus maniculatus*) is the host for hantavirus in southwestern USA.

the only hantavirus known in the USA was the supposedly harmless Prospect Hill virus.

Table 4.1 and Figure 4.3 show some of the other examples, Hantaan in Korea is from where the hantaviruses are named. There is also a Seoul virus and a very common one in Europe called Puumala virus, but compared with the North American form they are much more deadly. The New World forms are not as deadly, but they are much easier to catch, which is very important in an organism that only has a 30 000 base pair genome. We wondered if this was a new strain and we compared the evolutionary tree with other samples. We actually went back into frozen archives and were able to locate this virus with essentially the same sequence from museum specimens that had been stored for some time, so it was not a new mutation, it had just been missed over the years. One might ask how that happened. It turns out that it has been missed all over the world and it is therefore going turn up at other places for the same reason. Without going into all the details of the phylogeny for the rodents,

Table 4.1 The hantaviruses as known in 1993.

	Virus type			
	<i>Hantaan</i>	<i>Seoul</i>	<i>Puumala</i>	<i>Prospect Hill</i>
Location	Asia	Asia	North Europe	USA
Reservoir	Striped field mouse	Rat	Bank vole	Meadow vole
Pathology	Renal	Renal	Renal	Not known
Mortality (%)	5–15	1	1	

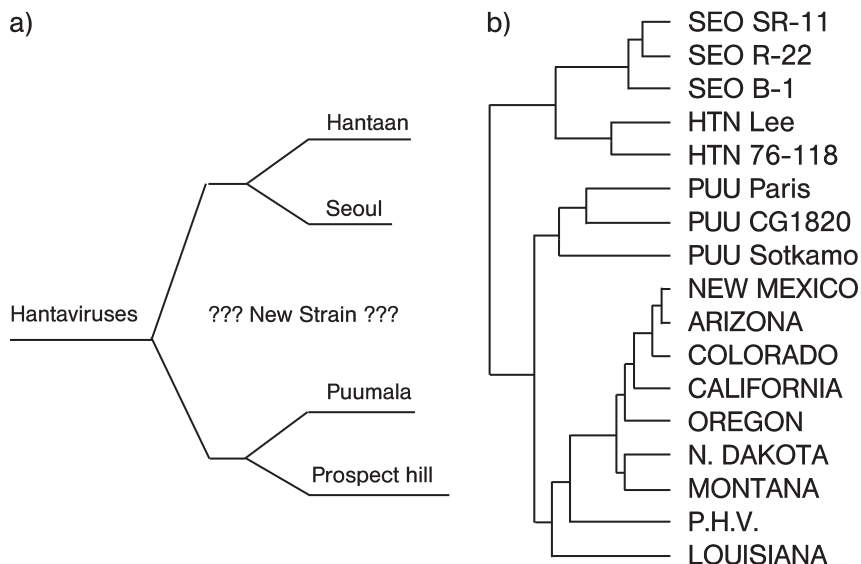


Figure 4.3 Evolution of the hantaviruses.

(a) Known hantavirus species and their relationship as of 1993.

(b) Currently identified species of hantavirus.

they are all species of rodents and if we take the known hantaviruses that occur in these rodents and compare the tree, one of the amazing things is that there is almost branch for branch concordance (Figure 4.4). Hence these viruses have been co-evolving with their rodent hosts for some time. In fact what we know for the New World is that these rodents came into North America about 20 million years ago, and it is thought that they brought the virus with them, since it is still present in Europe and Asia, and then it spread into South America and radiated throughout those areas.

In support of the earlier hypothesis that we know very little about biological diversity, even at this level with very pathogenic organisms for humans, remember that in 1993 there was only one known hantavirus in all of the New World. Today it looks like Figure 4.5 and we are finding new “species” every week or two. They are coming up very quickly and we are able to find them from the phylogenetic tree or the evolutionary tree for the rodent hosts predicting that they should have hantaviruses in them. Basically all of those that are shown in bold in Figure 4.5 are known to be pathogenic to humans. There is some evidence that there may be person-to-person transmission now in South America. All of these pathogenic forms in North and South America, and Central America also, have a mortality around 40% and so this makes this a very troublesome virus even though not huge numbers of people have caught it thus far.

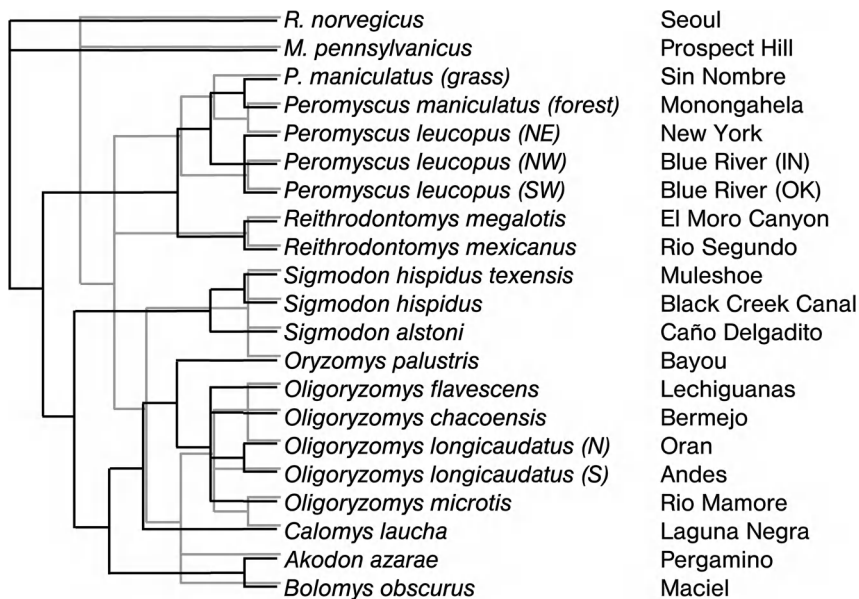


Figure 4.4 Overlay of the evolutionary relationships of hantaviruses and their rodent hosts. (Source: Plyusnin and Morzunov, Curr. Top. Microbiol. Immunol. 256, 47–75, 2001).

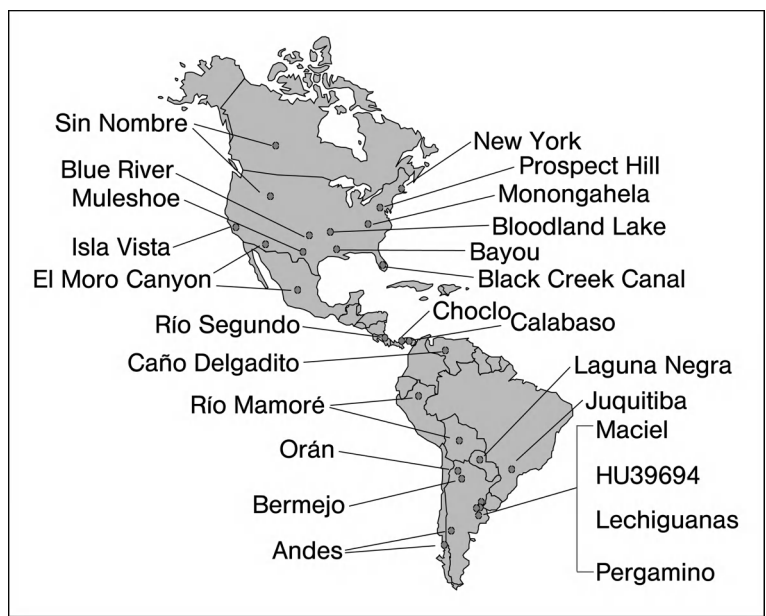


Figure 4.5 Pathogenic and non-pathogenic hantavirus species in the Americas. A boldface name indicates that the virus is known to cause illness in humans.

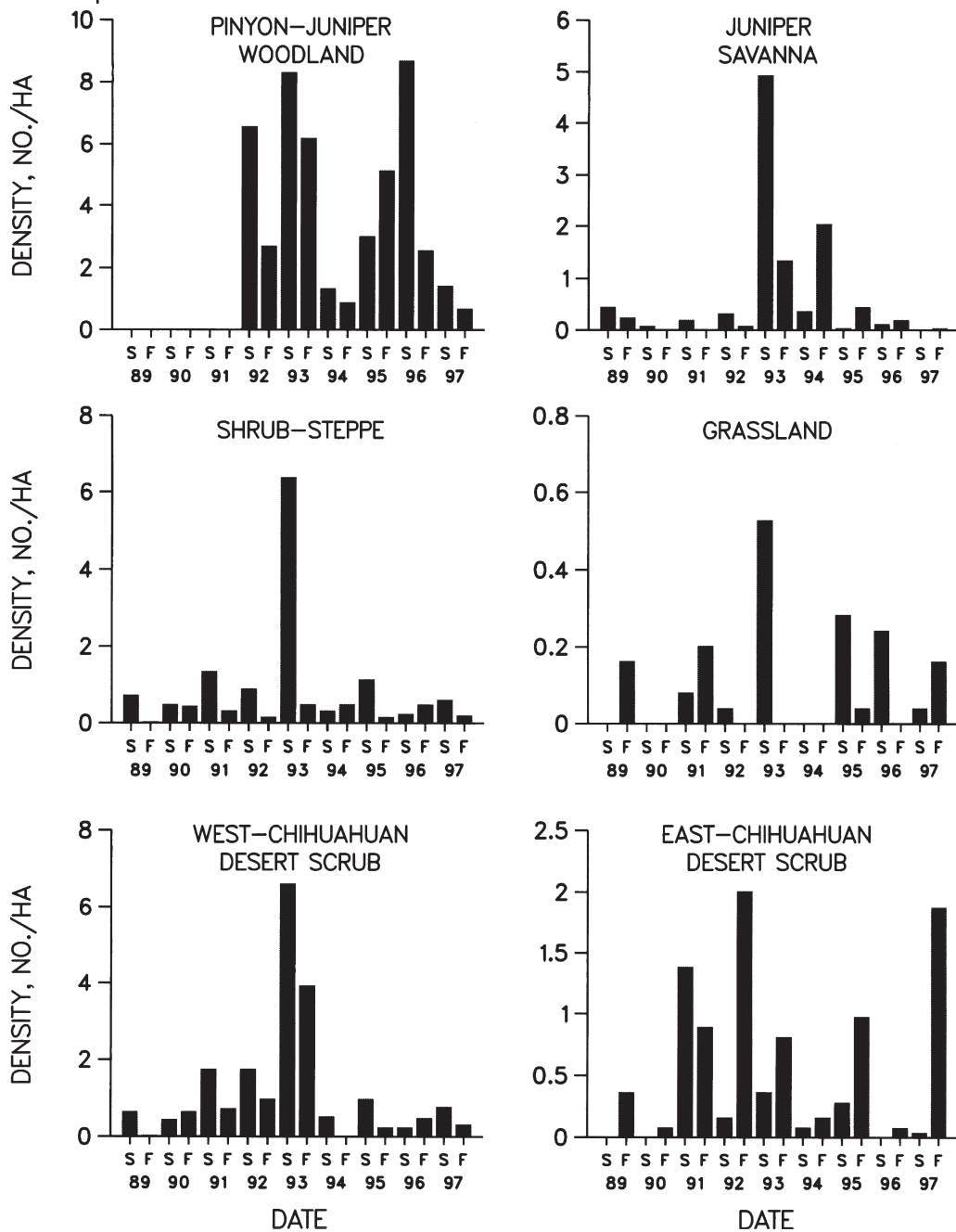


Figure 4.6 Population density of deer mice (in animals per hectare) recorded in different habitats within the Sevilleta wildlife refuge. Animal counts were made twice per year, once in spring (S) and once in fall (F).

4.5

Human Risk

The above did not explain why there was an outbreak in 1993 and so, in looking for evidence now that we know that these viruses exist and something about their evolutionary history, can we predict human risk in advance? We turned to a long-term study at the Sevilleta National Wildlife Refuge, where different ecosystems meet, going from a desert habitat to a pine and juniper kind of habitat, with many trees, bushes and shrubs that have good food resources for rodents. We wished to establish what was different about 1993. Was there anything different environmentally that would help to explain why there was an outbreak? We monitored how many mice there are across the landscape, and the data in Figure 4.6 represent mice per hectare. It can be seen that in all of these different habitat types in 1993 there were a lot more mice than there were in previous years. In looking for causes of what might have led to that, we investigated whether there is any relationship between rodent numbers and El Niños.

4.6

Environmental Factors

During the normal climatic cycle in southwestern USA most of the rainfall comes in the form of summer monsoons, although they are less intense than in some other parts of the world. Nevertheless, the characteristic precipitation events are very much like real monsoons: if we say there is a 40% chance of rain that means there is a 100% chance that it is going to rain, but it only rains in 40% of the places in the southwest. However, during El Niños that cycle changes and there is a lot of late winter and early spring precipitation in the form of snow at higher elevations and rain at lower elevations, and that has a profound impact on what occurs.

In terms of trying to model these climate fluctuations and disease outbreaks, we basically hypothesized that a trophic cascade was involved. Simply put, if there was a weather input in the form of precipitation that caused a change in plant primary productivity which provides food for rodents, that would increase rodent populations, which then had a linkage to human disease (Figure 4.7). We therefore carried out remote sensing to study this effect across the landscape with time and considering the sites in southwestern USA (Figure 4.8), one of the results was that that a simple correlation did not exist and in fact it became non-linear at some point. The general trophic cascade did exist, but there was an additional lag in this trophic cascade. In Figure 4.9, the bars indicate the numbers of human cases of hantavirus pulmonary syndrome starting in 1994. The diamonds show the numbers of mice per hectare and

Reservoir studies ➡ Predictive model

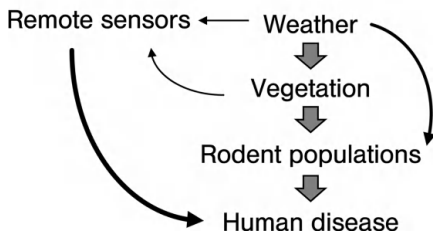


Figure 4.7 General model for predicting the risk for human hantavirus disease from environmental factors.

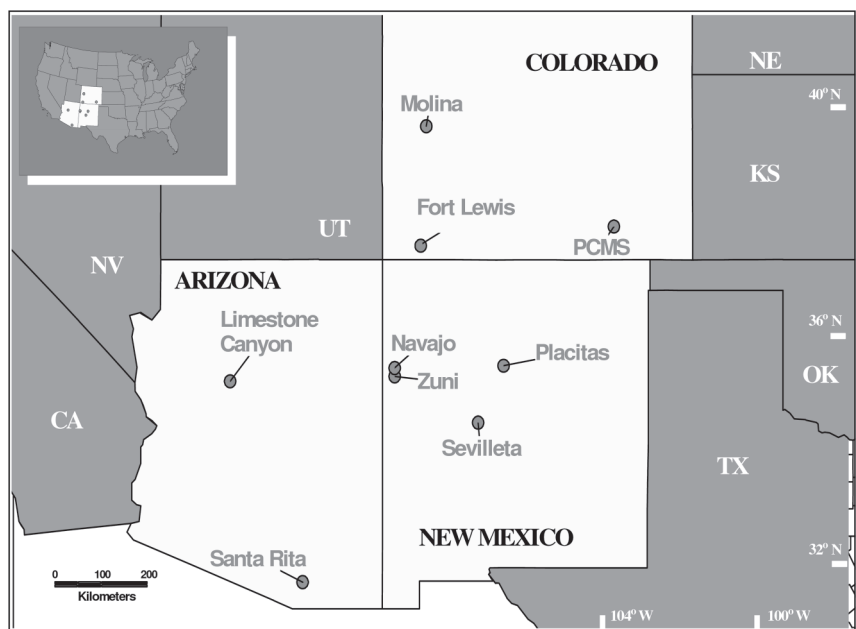


Figure 4.8 Sites in southwestern USA where the link between the rodent population and hantavirus outbreaks has been studied.

the squares indicate that the numbers of infected mice per hectare show a marked lag. It turns out that El Niños have been occurring at a higher frequency at least over the last few decades. In the spring of 1997 there was an El Niño event and there was a high precipitation input. The rodent populations responded remarkably to that event across the landscape and the numbers of mice went up to incredibly high levels: whereas one would expect one mouse per hectare on average, the number rose to over 20 per hectare just in this one

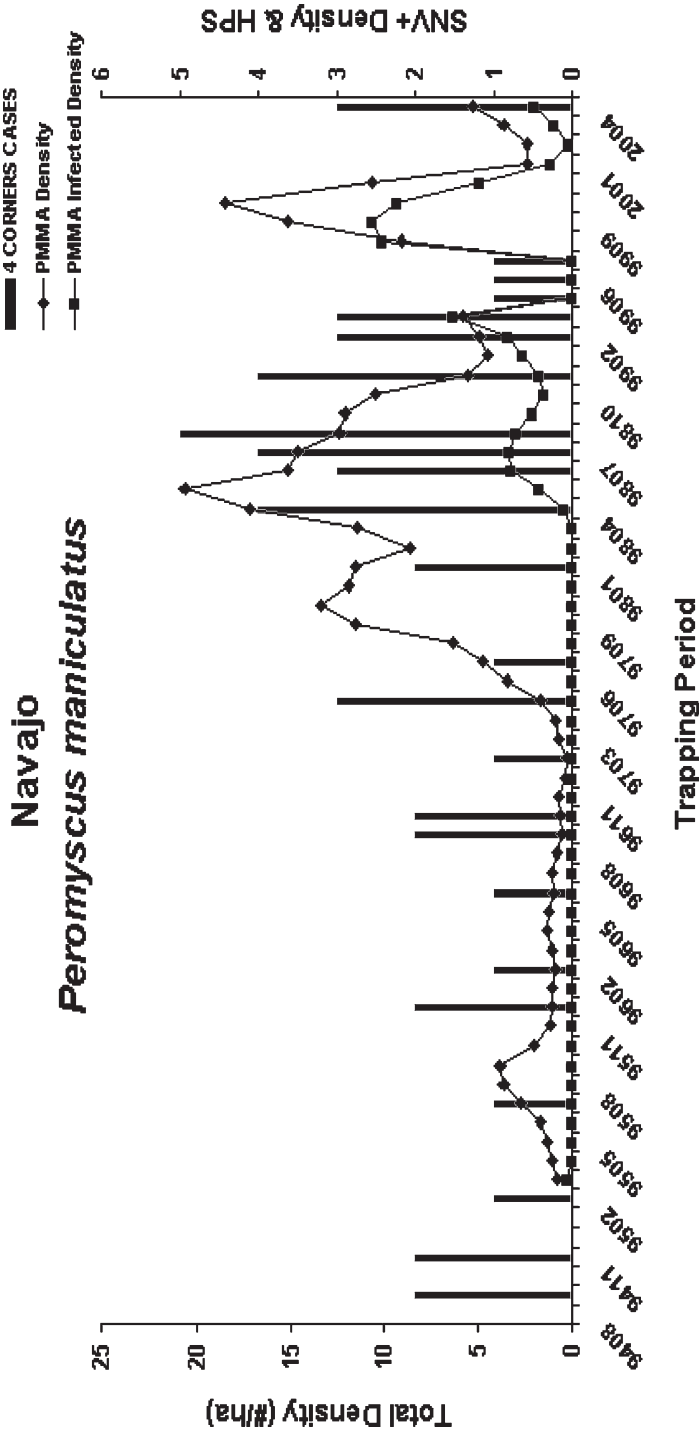


Figure 4.9 Data for one site in New Mexico. The density of deer mice (diamonds) and of infected mice (squares) over the period 1994–2004 is shown. The bars show the number of hantavirus pulmonary syndrome cases in humans in the area around the site.

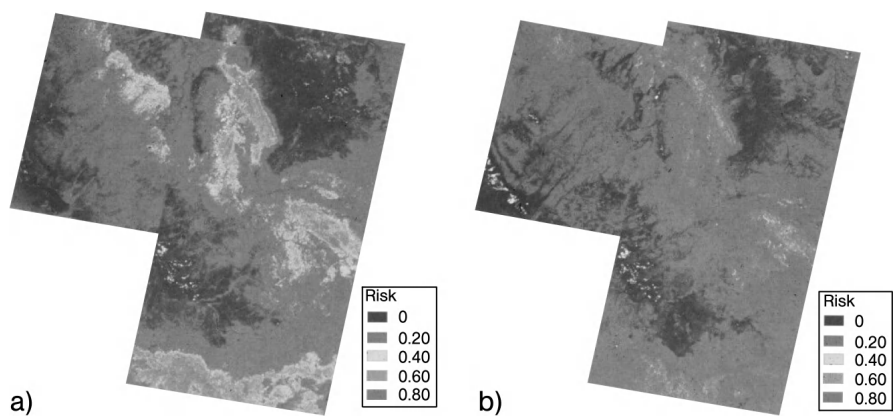


Figure 4.10 Prediction of high-risk areas for hantavirus pulmonary syndrome in southwestern USA. Results are given for two years, (a) 1993 when there was an outbreak of the disease and (b) 1995 when no cases were reported.

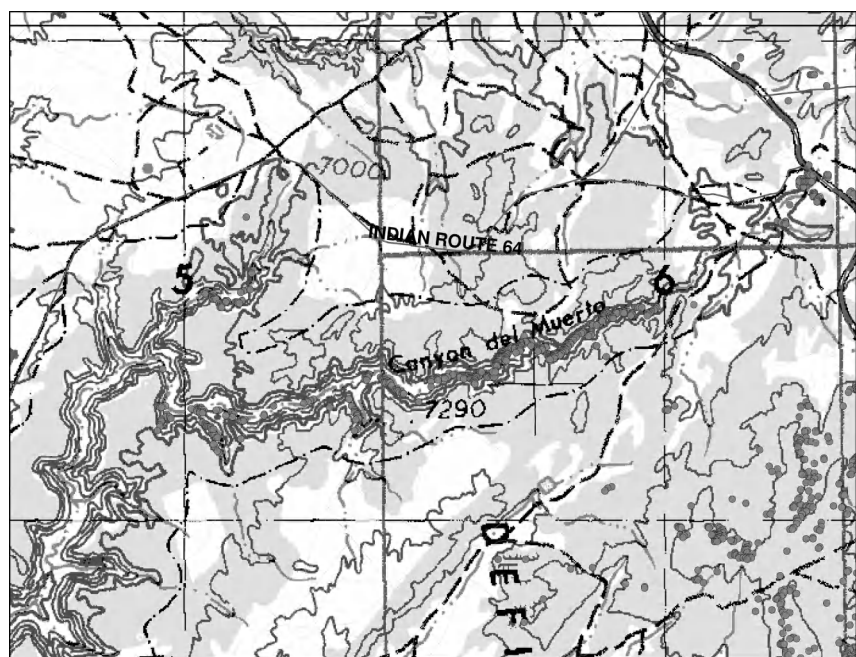


Figure 4.11 High-resolution map of the Canyon del Muerto site with predicted hantavirus refugia indicated by dots.

species. The number of human HPS cases, however, actually started to increase once the rodent population had started to collapse again. So, basically, there was a lag time of over a year before this started to affect the human population and even carried over into the second year. Hence we are essentially using this approach to model the hantavirus risk one to two years in advance in the areas where it occurs. This is a 170 000 hectare area with a model developed using remote sensing, with a trophic cascade hypothesis involving plant productivity that shows the risk in different areas.

Figure 4.10a shows the conditions in 1993, so this is a retrospective capture from that original outbreak. In 1995 when there were no cases for that same year, Figure 4.10b shows what the map looks like.

Considering a specific area, the Canyon del Muerto, each of the dots in Figure 4.11 represents an area where the virus hides in what we call refugia when there is no outbreak occurring. When the conditions are poor, there are still certain places that maintain a high viral load and we can identify those and then predict how the virus is going to spread from those areas.

4.7

The Importance of Biodiversity

Let us consider a further aspect of this climate outbreak model. Even though we are using the hantavirus, which is directly transmitted from rodents to humans, this could work equally well for any zoonotic disease that infects people or animals or whether there is a vector involved. We then asked the question, does biological diversity matter? The way this virus spreads into the environment is almost like “big bang” reproduction in plants: a lot of copies of the virus are made, it is spread into the environment and if it reaches the wrong host it can still grow and survive, but it will not be able to replicate and be passed on. We therefore hypothesize that if there were less diversity in the viral host that should be more dangerous than if there were greater biological diversity, in which case the virus would reach the wrong host more frequently on average.

Preliminary studies in several areas of Panama, which I will not discuss here in detail, bear out this notion, showing that the number of rodents actually infected with the virus increased when the biological diversity in the ecosystem decreased. Hence not only can climate factors cause a higher risk in human populations, but the way in which humans are influencing ecosystems, e.g. by land use, also makes a difference. All of these factors can combine to create novel hot zones for virus outbreaks.

4.8

Conclusion

A final thought is that all of our increasing knowledge of these infectious diseases has essentially ruined biological field trips. Figure 4.12a shows an example of what a field trip used to be like in the 1970s, where you have people eating and dead mice on the table and a little beer in the background. Today that same field trip looks like the photograph in Figure 4.12b and is not nearly as much fun.

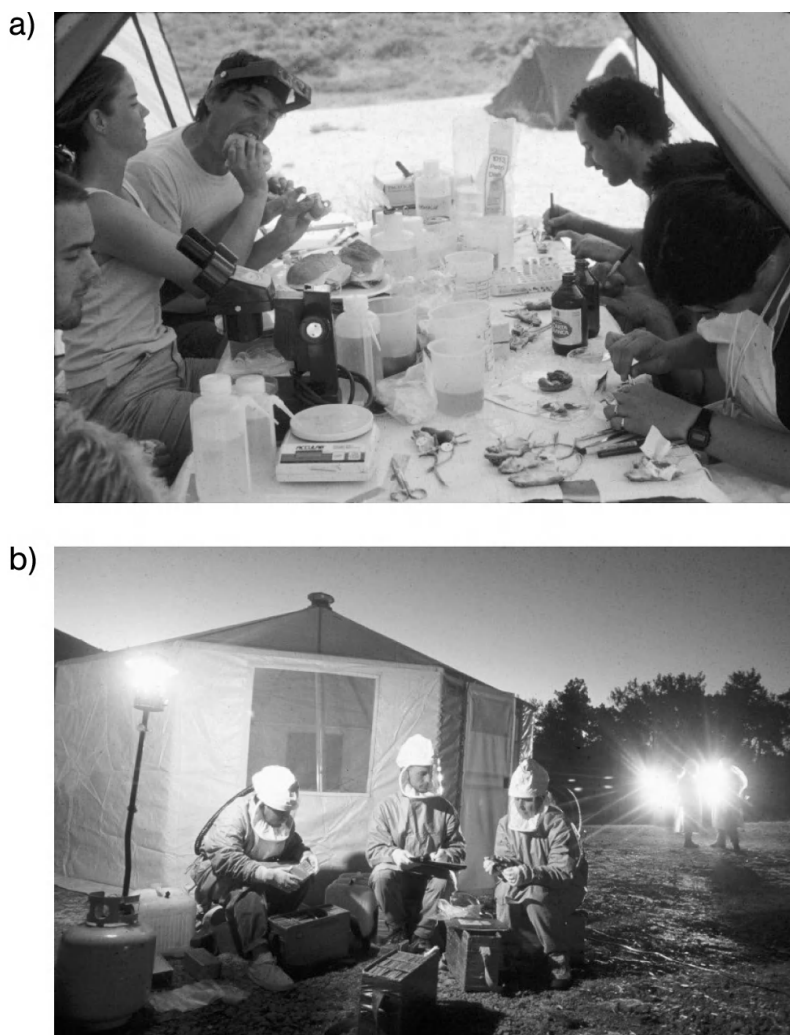


Figure 4.12 A microbiologists' field trip 30 years ago (a) and today (b).

Author Biography

Tony McMichael



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Professor Tony McMichael is Director of the National Centre for Epidemiology and Population Health, at The Australian National University, Canberra, and Professor of Population Health at that University's Medical School. During 1993–2001, he was Professor of Epidemiology at the London School of Hygiene and Tropical Medicine, UK. Upon returning to Australia in 2001, he received a 5-year Burnet Award (for personal research support) from the National Health and Medical Research Council.

Tony McMichael has over 30 years of experience in epidemiological research, with a particular interest in the study of environmental influences on the risk of disease. During 1993–2001, he chaired the assessment of health impacts for the UN's Intergovernmental Panel on Climate Change (IPCC).

During 2001–2005 he has played a leading role in the assessment of health impacts for the international Millennium Ecosystem Assessment (MA) Project. He was senior editor and author of "Climate Change and Human Health: Risks and Responses", published in 2003 by the World Health Organization (with WMO and UNEP). During 2004–2005 he was a member of the 15-member International Climate Change Taskforce, whose report on a universal, flexible, post-Kyoto strategy was released internationally in January. Currently he is co-chairing the development of the "Global Environmental Change and Human Health" project, within the Earth System Science Program of the International Council of Scientific Unions/IGBP/IHDP/Diversitas consortium.

5

Climate Change and Human Health: the Sharp End of “Sustainability”

Tony McMichael

5.1

Introduction

Epidemiology is the study of patterns of disease in human populations, the study of their causes and, of course, the study of how best to reduce or prevent them. I have been involved in this area for about the last 15 years and in particular have been coordinating the assessment of the health impacts of climate change for the UN's Intergovernmental Panel on Climate Change. This chapter presents a broad overview of how we are approaching this topic area, the types of things that we are beginning to understand about it and the ways in which we attempt to estimate the future impacts of scenarios of climate change. It includes the social or political dimension, and the question is raised of whether this sort of topic represents the sharp end of the sustainability discourse. There has been a lot of rather blunt or unfocused discussion about sustainability. Following Kul Gautam, the Deputy Director of UNICEF, I believe that human population health is at the core of sustainability and that argument is made both at the beginning and at the end of this chapter.

5.2

Global Warming

This section gives a brief summary of what we know today about global warming. Matters have been clarified enormously over the last quarter of a century as climate science has come to grips with this potentially momentous change that we humans are inducing into the world's climate system. The greenhouse gases naturally warm the Earth's surface by about 32 °C, thus preventing it from freezing over. Much of the warming is due to carbon dioxide and we know that the concentrations of that greenhouse gas have increased

by over one-third in the last one or two centuries as a result of industrial and agricultural activity. There are still some uncertainties, of course, about the science in this area. There are things we do not understand about the ways in which the world's climate system will respond in future to continuing changes in atmospheric composition, nor, of course, can we know exactly what the trajectory of future emissions will be.

There is now a very clear consensus, close to unanimous agreement, amongst climate scientists that rising greenhouse gas concentrations are going to cause further warming, estimated to be of the order of 2–3 °C on average during this century, rather more at higher latitudes and less at lower latitudes. Interestingly, it is now understood from fingerprinting the details of the pattern of warming over the last half century that most of it is actually attributable to the extra greenhouse gases that we the human species had injected into the lower atmosphere.

5.3

Climate and Human Health

After the above review of where climate science itself has now got to, we can consider why we might be interested in estimating the risk to human health. There are three reasons. The first is really the major policy-related issue that bears on the issue of sustainability. We need actually to understand what the range of consequences of global climate change is likely to be for humans and for those systems upon which we depend. Hence we want to understand better the magnitude of all these future risks. That is of interest to scientists, of course, but it is particularly important to inform and to enrich the policy debate so that we actually know what we are talking about and what sort of future risks we are engaging with.

Second, such an assessment provides a basis for national and local governments and communities to begin to think about the sorts of risks that they will face and what sorts of preparedness and what sort of adaptive responses might be appropriate. If you are living on a small island state, what do you do about the rising sea levels? If you are living in large urban agglomerations subject to intense heating during summertime, what might be appropriate with respect to future urban planning, house design and human behavior with respect to extremes of heat, heat waves in summer and so on?

Third, of course, learning more about this will help to facilitate early warning systems. Terry Yates in Chapter 4 has given us a very good example that is related to the El Niño cycle, which we believe is being intensified now by the process of global climate change. That would be a good example of where, if you understand the basic ecology and biology, you are actually in a position to make useful predictions that would lessen the human case load. These were

all good reasons for understanding these relationships, but again the point should be made that we in particular need to enrich our understanding of what we are doing to the Earth and what the consequences might be for the life support systems upon which human well-being and human health depend. This is what is meant here by the sharp end of sustainability.

5.4

Environmental Changes

There are a lot of large-scale environmental changes now being documented around the world, and all of these reflect the aggregate pressures that we are putting on the Earth's systems as function of human numbers and intensifying economic activity. The range of the sorts of health impacts that we are concerned about is outlined in Figure 5.1, and they have been arranged in three categories of direct, ecosystem-mediated and indirect health effects. Some impacts are predictable: if you have an increase in flooding or an increase in heat waves, there will be direct effects on human health and human survival. More interesting are effects that arise via disturbances of ecosystems, for example, affecting patterns of infectious disease, and of course that whole

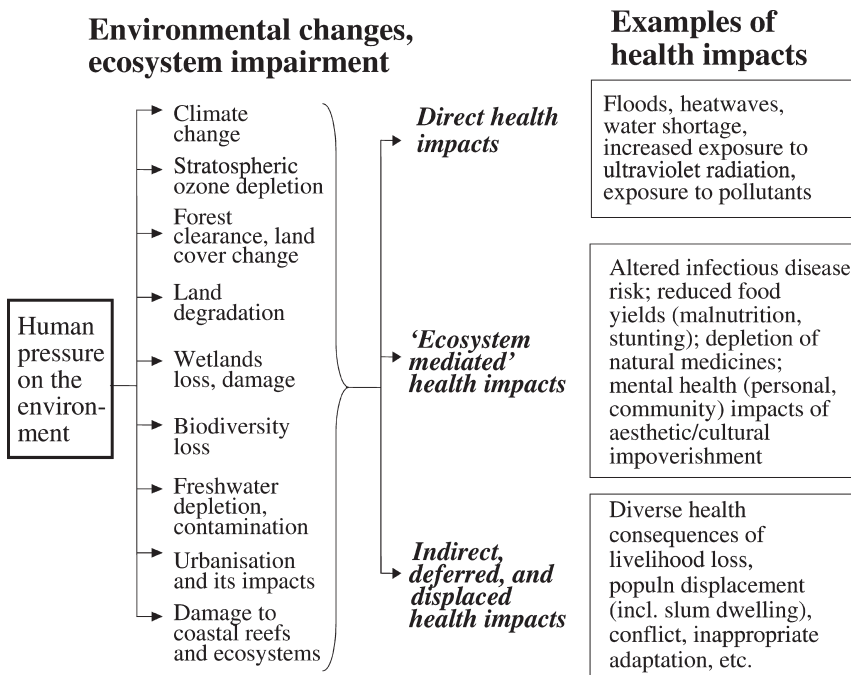


Figure 5.1 Anthropogenic environmental changes and their impact for human health.

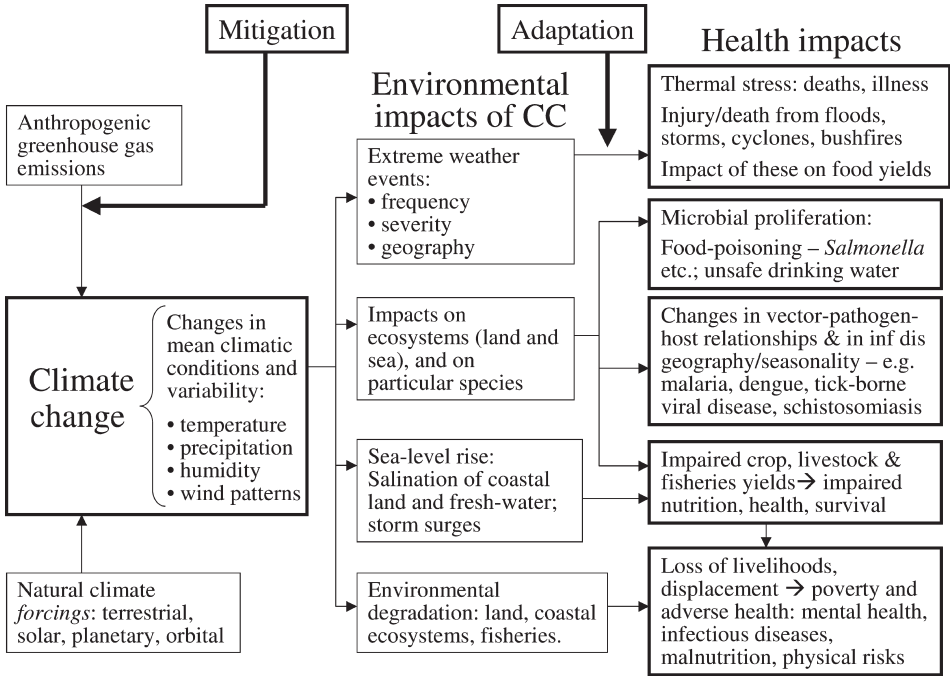


Figure 5.2 The potential results of climate change and global warming.

penumbra of potentially very important impacts due to economic, social and demographic dislocation.

Let us take the top item on the list, climate change, and examine it in more detail. The left part of Figure 5.2 demonstrates that the world’s climate is influenced by a number of natural climate forcings and they will continue; there will always be a variability, but in addition we are imposing this extra anthropogenic forcing on the climate system which is then manifested in these various changed characteristics. Our first option, of course, in terms of mitigation of societal responses is to reduce greenhouse gas emissions, and this is the primary need.

Climate change will be manifested in various forms in terms of environmental impacts and environmental changes, as shown in the middle of Figure 5.2. Again, the simple ones are at the top: the extreme weather events, the impacts on ecosystems, the sea-level rise and its various consequences around coastal regions and other environmental degradations occurring as a result of climate change, such as the drying out of soils in some agricultural regions. On the right are listed the health impacts, those which occur fairly directly as a result of extreme weather events, for example, the various health risks that result from this more complex process of changing ecological

systems, relationships between species and so on, increased temperature affecting microbial proliferation, leading to food poisoning, unsafe drinking water, changes in vector–pathogen–host relationships, affecting diseases such as malaria, dengue fever, tick-borne viral diseases and schistosomiasis. Many of these diseases are very sensitive to climatic conditions, particularly the vector-borne diseases where there are small species such as mosquitoes or ticks that have their own thermal maintenance mechanisms and are very sensitive. There are effects on food production and then that final category again involving this wider penumbra of health-endangering changes in livelihoods, population displacement, all of the things from which refugee populations typically suffer. Hence our secondary response, if we cannot stop the flow of greenhouse gases or even as we are doing that, is to think about the ways in which these impacts can be lessened through adaptation.

5.5 Examples

After the above background discussion, we can consider some examples. In 2003, there was a major heat wave that affected much of northern Europe, and Figure 5.3 shows the figures for Paris, i.e. the temperature chart, the daily maximum temperature and the daily minimum temperature over this 2-week period, and the rise in the numbers of daily deaths can be seen.

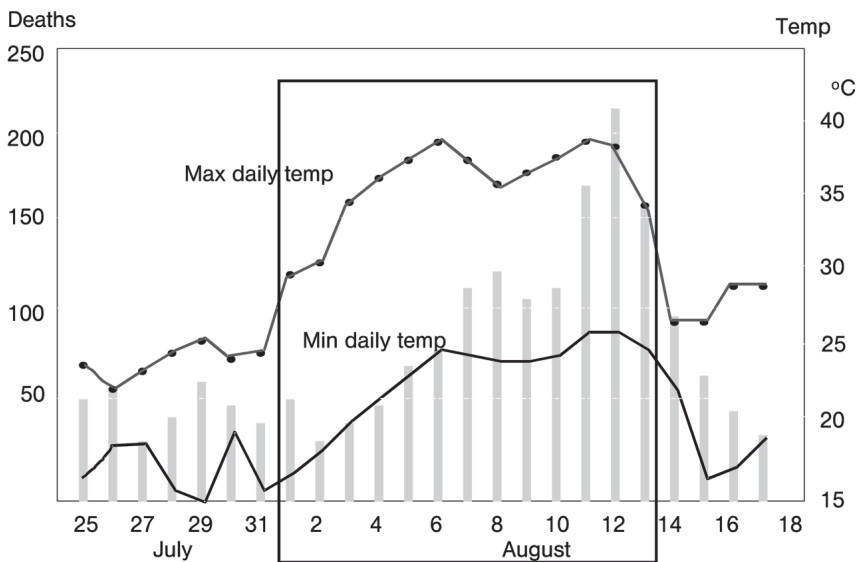


Figure 5.3 The 2003 heat wave death toll in the greater Paris area.

In greater Paris there occurred an estimated 11 000 excess deaths statistically during that period, an extraordinarily large mortality toll. It is from this sort of experience that we learn about the relationship between daily temperature and risks of mortality. Some recent work has looked in detail at the effects of heat waves (Stott et al., *Nature* 432, 610–614, 2004) and it was estimated that the human-induced warming in Europe since the 1970s has more than doubled the probability of this sort of event occurring. Historically, such an event has occurred about once in every 400 years. Interestingly, it is estimated that by the middle of this century it will be occurring about once in every 4–5 years, about a 100-fold increase as a function of the climate change process.

That raises questions as to what the impacts might in the future of the regime of heat waves, and Figure 5.4 shows a typical relationship between the number of daily deaths and the daily temperature. It can be seen that there is a sort of “comfort zone” where the number of daily deaths is at minimum. Daily deaths rise as the weather becomes warmer, which would well describe the experience of London and probably Paris. If we shift the range of an annual temperature slightly the right by warming by 2–3 °C, then we might expect there to be some shift in the minimum due to some physiological and behavioral adaptation. Thus the comfort zone moves slightly the right, but the basic shape of the graph remains unchanged and from this one can estimate how many more heat-related deaths will occur in the future and how many fewer cold-related deaths might occur and calculate the net change.

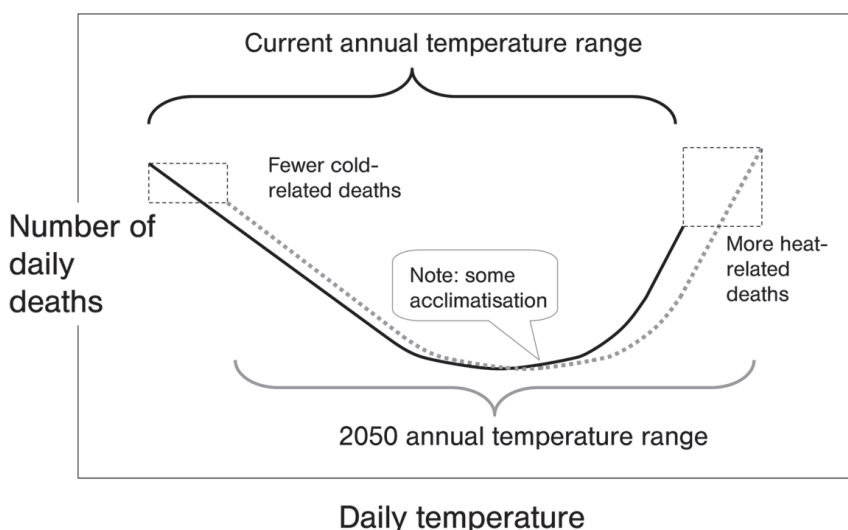


Figure 5.4 Impact of an increase in the average temperature on the annual number of deaths in a temperate-zone population.

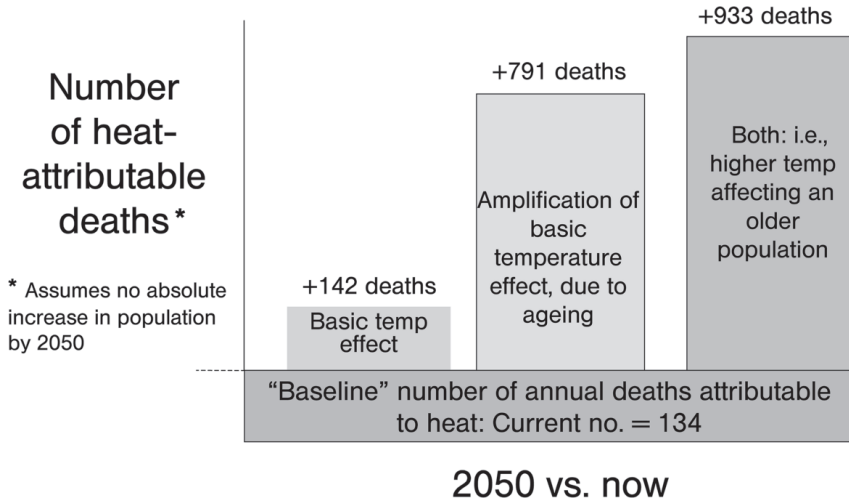


Figure 5.5 Estimated additional heat-related deaths in the city of Brisbane under alternative climate scenarios for 2050, as predicted by the CSIROmk2 model. (Source: NCEPH/CSIRO, 2003).

We did that in Australia about 2 years ago, funded by the national government, estimating for the middle of this century the additional heat-related deaths due to higher mean annual temperatures. We are working with the national industrial scientific organization CSIRO and in Figure 5.5 for the city of Brisbane on the northeast coast it can be seen that over the last few years the average number of heat-attributable deaths due to extremes of heat in summer has been around 134. We estimate that if the population did not change in size or age, there would be a similar additional number by 2050, but because of population aging and the population becoming more susceptible to heat, in fact the number of additional deaths would be considerably more amplified by the aging process, so we are actually talking about a seven- or eight-fold increase in the estimated future number of annual deaths in Brisbane. This estimation makes various assumptions, of course, about lack of adaptation, but at least gives an indication of how we can do some simple modeling of the likely increase in risks. We have done similar work on dengue fever and other mosquito-borne diseases. Viral infection is widespread around the world, and has been on the increase, generally in the last few decades, not necessarily because of climate change, but also because of increased trading and tourism patterns and a relaxation of public health controls, particularly in central and south America.

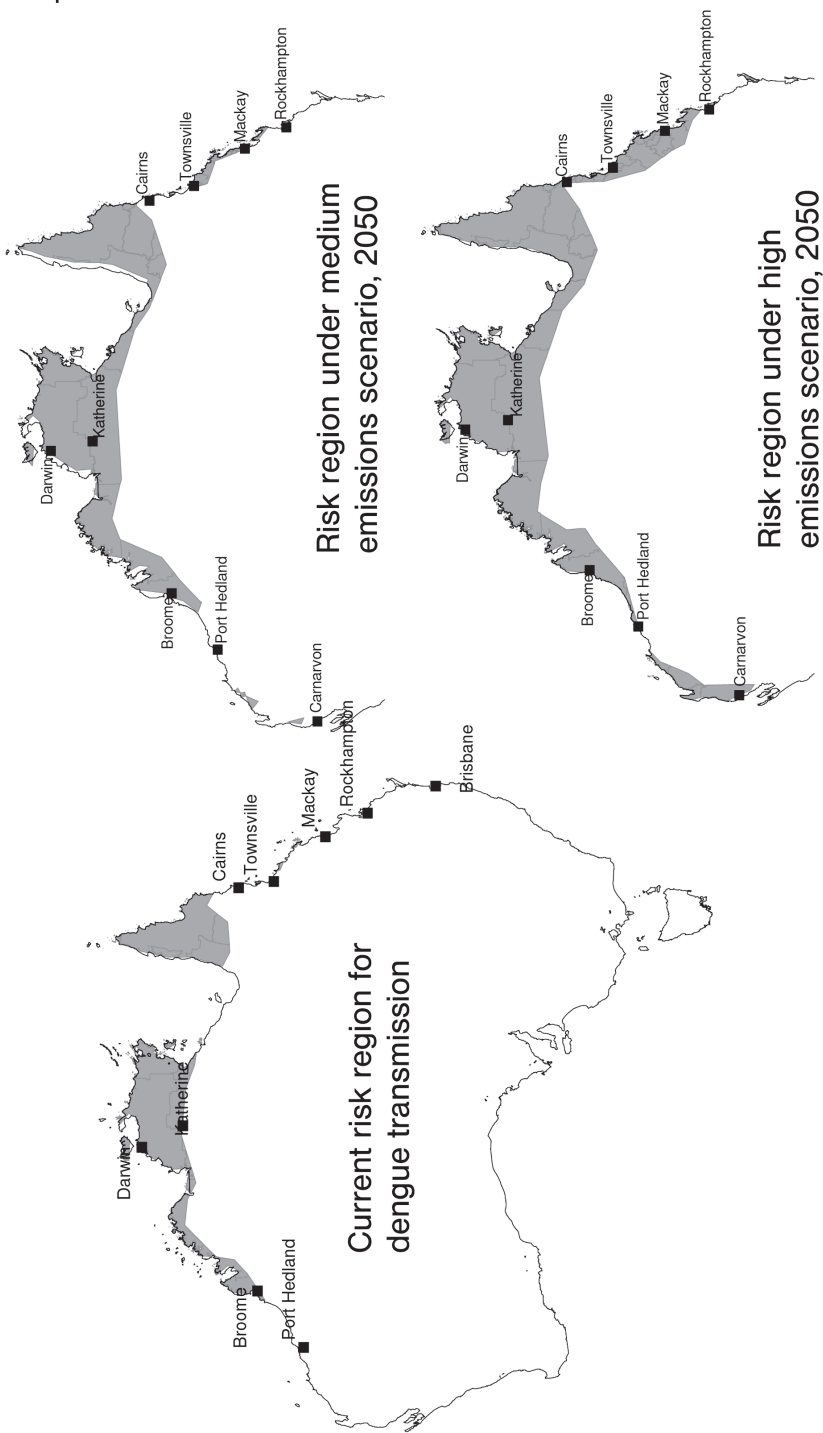


Figure 5.6 Estimated spread in the geographic area suitable for maintenance of *Aedes aegypti*, the vector of dengue fever, under alternative climate scenarios for 2050. (Source: NCEPH/CSIRO, 2003).

Figure 5.6 shows where this disease can be spread in Australia at the moment, in terms of where the mosquito can survive as a function of temperature, rainfall and humidity. We have estimated for a medium greenhouse gas emission scenario and the associated temperature rise and rainfall change in Australia where this vector could actually transmit the disease in 2050, and then we took a similar approach for a higher emissions-related climate change scenario. This does not tell us where the disease will be, but it tells us where it could be in the future and that is important for us to begin to understand.

This is an example again of using our empirical knowledge, our understanding of relationships between disease and climate, to model how a change in climatic conditions would affect the patterns of health risks in future. Similar work is being done at the London School of Hygiene and Tropical Medicine on the transmissibility of malaria in Europe, because malaria was widespread in Europe until it began to be eliminated during the 19th century. The last case occurred in England, for example, in the 1950s, so it had a long presence in Europe, currently essentially eliminated except in southeastern Europe. It occurs in Turkey, but under current climatic conditions that is where this malaria vector mosquito can transmit the disease in principle. Figure 5.7 is an estimated map showing where that particular malaria vector would spread to within Europe in the 2080s. Again, this does not necessarily predict what will happen, but it gives us a feel for the sorts of risks that we are now starting to engage with as we allow the world's climate to undergo this change.

Food production is also at risk rather variably around the world. We are talking about a future world of winners and losers and Figure 5.8 shows a typical relationship between photosynthetic activity and temperature from which it can be imagined that if in today's world you live in certain parts of Canada, the Ukraine or northern China, then some more warming would be good for you. Photosynthetic activity would increase slightly, but if you are living in northern Africa, much of southern Asia, parts of Central America and southern China, more warming would be bad for agricultural yields, and that indeed is what the modeling has generally shown for this coming century, namely that there will be substantial gains and substantial losses in different regions, but overall a net loss in cereal grain production in the second half of this century. Although not spectacular, it will be of the order of 3–5%, affecting particularly food in secure populations unless we achieve a fairer world by then.

The final example is one of the more diffuse impacts via sea-level rise and flooding and the effects on local populations, in terms of physical hazards, infectious disease risks, displacement of populations, local food production and so on. It can be seen in Figure 5.9 that for these three different greenhouse emission scenarios and associated sea-level rise changes the sorts of numbers of persons in the Pacific Island regions who we have estimated would be at some risk.

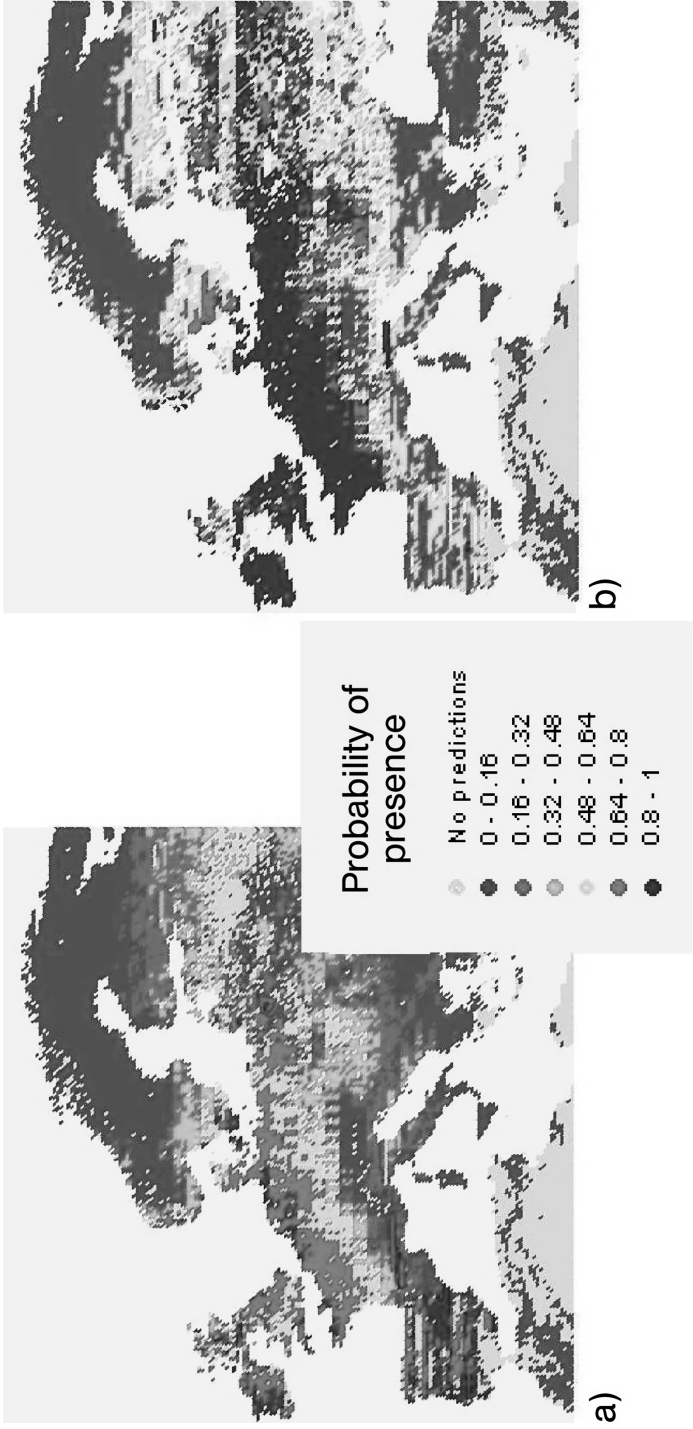


Figure 5.7 Predicted distribution of the malaria vector *Anopheles atroparvus* in Europe. (Source: Kuhn et al., J. Med. Entomol. 39, 621–630, 2002).

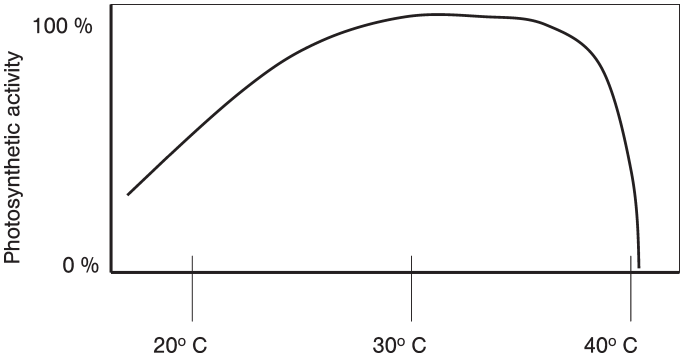
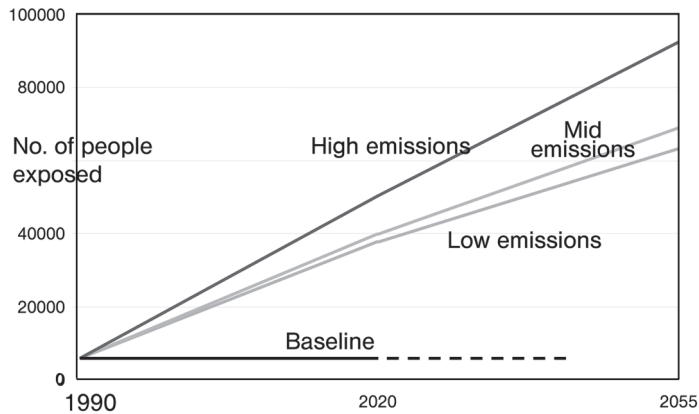


Figure 5.8 Impact of ambient temperature on photosynthesis.



Baseline (1961-1990 climate); low = +19cm; mid = +45cm; high = +80cm

Figure 5.9 Number of people exposed to coastal flooding for the Pacific Islands under alternative climate scenarios for 2020 and 2055. (Source: NCEPH/CSIRO, 2003).

**5.6
Conclusion**

At this point we should consider what bioscience and biotechnology can do. We need to understand better, for example, how populations adapt physiologically to changes in prevailing temperatures. We need to understand more about how climate change affects the nutritional quality of foods. Then we can go on to lessen the health risks, e.g. by improved control of infectious agents and their vectors, by developing cultivars that are better adapted to the new climates, by using energy-efficient techniques for work, home and

transport, by using renewable energy and finally by enhancing population control in high-fertility countries.

Hence there are many interesting questions for us to approach within the realm of bioscience and biotechnology. We need to become better at quantifying the impacts; epidemiology will continue to work away at these sorts of things, estimating for the world at large the numbers of deaths currently attributable, for example, to climate change. We have made a first-order estimation recently with WHO, at least for these particular health outcomes, of what the 0.6 °C warming that we are currently experiencing relative to the historical past might be causing and likewise estimates are now proceeding as we did in Australia at the national level. The recent WHO estimate (from 2004) for deaths attributable to climate change is 160 000 cases for 2000 alone, caused by malaria, dengue fever, diarrhea, floods, heat waves and malnutrition. Economists are also beginning to become engaged and to think about the ways in which they might estimate the direct costs, the costs due to the lost productivity and other costs if we actually value human life beyond its productive capacity, and there are technical issues for health economists about how to estimate time-specific or the total accumulated economic costs and whether we should actually discount future impacts. One might make the argument that we should use negative discounting and value the future rather more than the present because we have a moral responsibility to that distant future. Yet on a conventional economic discounting 2050 does not count, it has disappeared on a 5% annual compound discount rate. Hence there are some interesting questions across the disciplines for us to address in getting a better measure of these things.

Finally, the major reason for our concern is that climate change provides the clearest signal yet that humans collectively are now exceeding the Earth's capacity and that the climate system is a crucial part of our life support system. It can be argued that the real measure of non-sustainability is the advent of systemic environmental risks to human well-being, health and survival. We want good environmental, good social and good economic conditions, not because they are important in their own right, but because they are the means of optimizing human experience including, of course, health and survival, and for the moment climate change reminds us that we are all on notice in terms of what we are now doing collectively to the Earth around us.

Author Biography

Steen Riisgaard



President and CEO, Novozymes A/S

Steen Riisgaard joined Novo in 1979 as a microbiologist in Enzymes R&D. In 1982 he went to Tokyo to start up an Enzymes R&D unit in Novo's subsidiary, Novo Industri Japan Ltd.

He returned to Denmark in 1985 as director of Enzyme Process Research and the following year was appointed vice president of the Detergent Enzyme Division.

In 1989 he was promoted to corporate executive vice president with special responsibility for Enzyme Business, including Enzyme Research, Enzyme Development and Application, Enzyme Production, Enzyme Operations and all of Novo Nordisk's activities in China.

Prior to joining Novo Nordisk, he was a research fellow at the Serum Institute of Denmark (1976–1977) and a research microbiologist at Foss Electric, Denmark.

Steen Riisgaard received his MSc in Biology from the University of Copenhagen. He serves on the boards of WWF (World Wildlife Fund), Denmark, The Copenhagen Centre – New Partnerships for Social Responsibility, and Egmont International Holding A/S.

6

White Biotechnology – For the Benefit of Climate and the Environment

Steen Riisgaard

6.1

Introduction

This chapter is intended to give at least a potential way-out in terms of mitigating climate changes and I am one of the firm believers in the case for white biotechnology in this respect. The case for white biotechnology will be illustrated using enzyme technology, in which Novozymes specializes.

It is well recognized that environmental issues are global issues that should concern us all. The simple background for this is that humans spent their first 10 000 years on using sustainable agriculture. This was then replaced with the industrial revolution, by 200 years of overuse of nature's resources and a green revolution that happened at a great cost to Nature.

White biotechnology can offer a new solution, a new way for industry to continue bringing economic welfare to human societies, but at the same time preserving Nature's resources and potentially, at least, preventing climate changes. Examples will be given of the what enzymes, what white biotechnology, can do: not the high-profile examples that people talk so much about, such as the fuel ethanol, but just small cases that they are all added up and if they are implemented widely, will have a profound effect.

6.2

The Lecitase Example

This section will consider the barriers to harvesting this potential and some initiatives that might be suggested to speed up the implementation of white biotechnology. The first example, one of out hundreds where we are doing a

lifecycle analysis (LCA) to test the case, concerns an enzyme, lecithase, which is a phospholipase that can replace the traditional chemical method of purifying soybean oil. Of course, when one carries out these lifecycle analyses, one has to take a holistic view of the total process, starting with the farming of the soybean and ending with the refined soybean oil, and looking, of course, at the waste stream generated, which has to be normalized, in this example on the output side, 1000 tons of soybean oil. We then compare the traditional chemical methods with the enzymatic method and since the impact is very much one of reduced need for input, then we see the impact at many places, not just where the change happens, in the oil refining step, but on all the individual process steps. Calculating the benefits as a CO₂ equivalent, it can be seen in Figure 6.1 that per 1000 tons produced the new process will save 44 000 kg of CO₂ equivalent.

Although not much in itself, one factory transformed into this processing, we are transforming factory by factory these days, gives savings annually of 12 000 tons (Table 6.1). If we are able to implement this approach widely, so that all soybean mills ultimately use this technology, the savings will be 1.3 million tons, and if we include also the similar oils, then they would be about 2.3 million tons. Again, this is not particularly great in itself, but this is just one example of one enzyme and we have 600 different types. The environmental benefits are not restricted to those of CO₂ emission. There is energy associated with CO₂, of course: acidification, nutrient enrichment, smog formation, and all these count (Table 6.2). The technology actually shows a better performance than the traditional chemical routes.

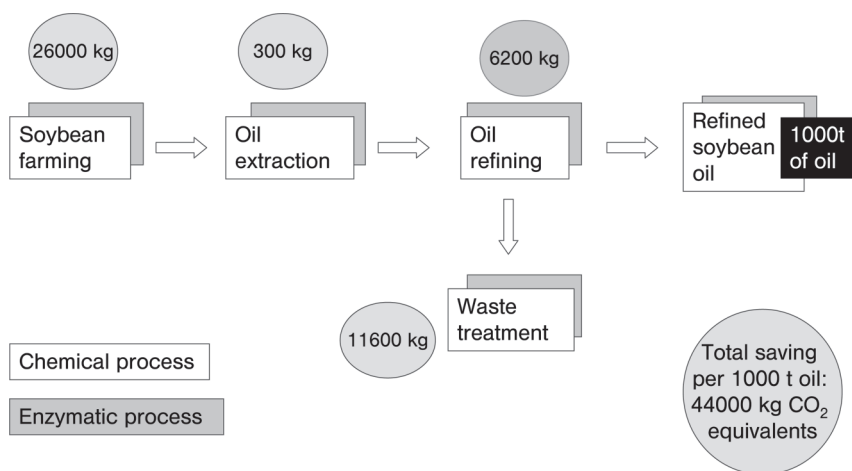


Figure 6.1 Eco-analysis of the whole process chain in soybean oil manufacture. Circles indicate the amount of CO₂ equivalents that is saved per 1000 tons of product, if one step in the oil refining process, chemical degumming, is replaced by an enzymatic process.

Table 6.1 Potential impact of substituting an enzymatic for a chemical process in the manufacture of vegetable oils in terms of reducing CO₂ emission.

<i>Savings from a single soybean oil manufacturing plant</i>	<i>Savings if total production of soybean oil applied enzymes</i>	<i>Savings if total production of soybean, rapeseed and sunflower oil applied enzymes</i>
12 000 tons CO ₂	1.3 million tons CO ₂	2.3 million tons CO ₂
Corresponding to annual CO ₂ emission from 1600 average world citizens	Corresponding to annual CO ₂ emission from 180 000 average world citizens	Corresponding to annual CO ₂ emission from 300 000 average world citizens

Table 6.2 Environmental impact of converting a single oil mill to an enzymatic process for degumming.

<i>Impact potential from one manufacturing plant</i>	<i>Savings from treatment of 288 000 t oil</i>	<i>Corresponding to the environmental load from</i>
Energy		700 people
Global warming	12 000 t CO ₂ equivalents	1600 people
Acidification	140 t SO ₄ equivalents	1400 people
Nutrient enrichment	100 t PO ₄ equivalents	4000 people
Smog formation	4 t Ethylene equivalents	250 people

The first conclusion here is that it is possible to improve the present methods, in an incremental fashion, and even if the OECD rightly points out that so far the incremental improvements have been insufficient, then it can still be argued that there is a case for them and there is a case for much more rapid implementation of the technologies that are already there.

If one looks at enzyme technology and wants to broaden the application area for industrial enzymes and for enzymes to have real impact, then of course many different industries have to be addressed, practically all the industries that we are engaged in today. It is also necessary to bring this technology into play not only for incremental changes but also for radical changes, where the whole value chain is radically changed. Finally, of course, we have to look at the technology: is the technology able to deliver the right type of enzymes capable of catalyzing the right type of processes, and can we do it quickly and economically? These points are addressed next.

6.3

Enzyme Technology

Examples are presented from the small company Novozymes, where we are working with enzyme technology. We have addressed some of the industries that we serve. Figure 6.2 shows that actually we are addressing a number of industries, not really deeply, but we are in contact with several and in each of these cases the use of 1 kg of enzyme actually gives rise to a good improvement in CO₂ emission, ranging from savings in the baking industry of 3800 kg per kilogram of enzyme, to only 30 kg in the animal feed area. However, in the animal feed area, the main driver is the reduction of phosphate pollution and not so much the efficiency of production.

We have many more industries that we serve and we have not had the time yet to do LCA on those. A conservative estimate has been used here, just extrapolating what we are seeing now with what just our small company contributes, and this conservative estimate indicates that for every kilogram of enzyme that our customers use, there is an associated saving of at least 100 kg of CO₂, and with 2004 production figures Novozymes contributed to a reduction of 13 million tons of CO₂, which happens to be what Denmark must save to live up to the Kyoto Protocol. Hence even in our small way and with the small impact that white biotechnology has so far, it does mean something with the combination of enzyme technology and white biotechnology. What could change the situation much more dramatically, of course, would be if we could achieve radical changes and the technology, as we see it, is there to change radically the value chains in certain industries.

So far, most of what we are doing involves incremental changes, in the short term, because economics demands that we earn money tomorrow and so we are going for the easy gains. To go for big radical changes, we need to tie up with governments, we need political support for that and we also need to tie up with agriculture and other industry players, but we believe that the technology is there to move from small incremental changes to radical changes (Figure 6.3). The only kind of example, that is beginning to look practical, is the use of waste biomass as an input to industry and as an input to fuel ethanol. This is where we use enzyme technology to generate fermentable sugars that can then be used as raw material input either for fuel ethanol or for industry.

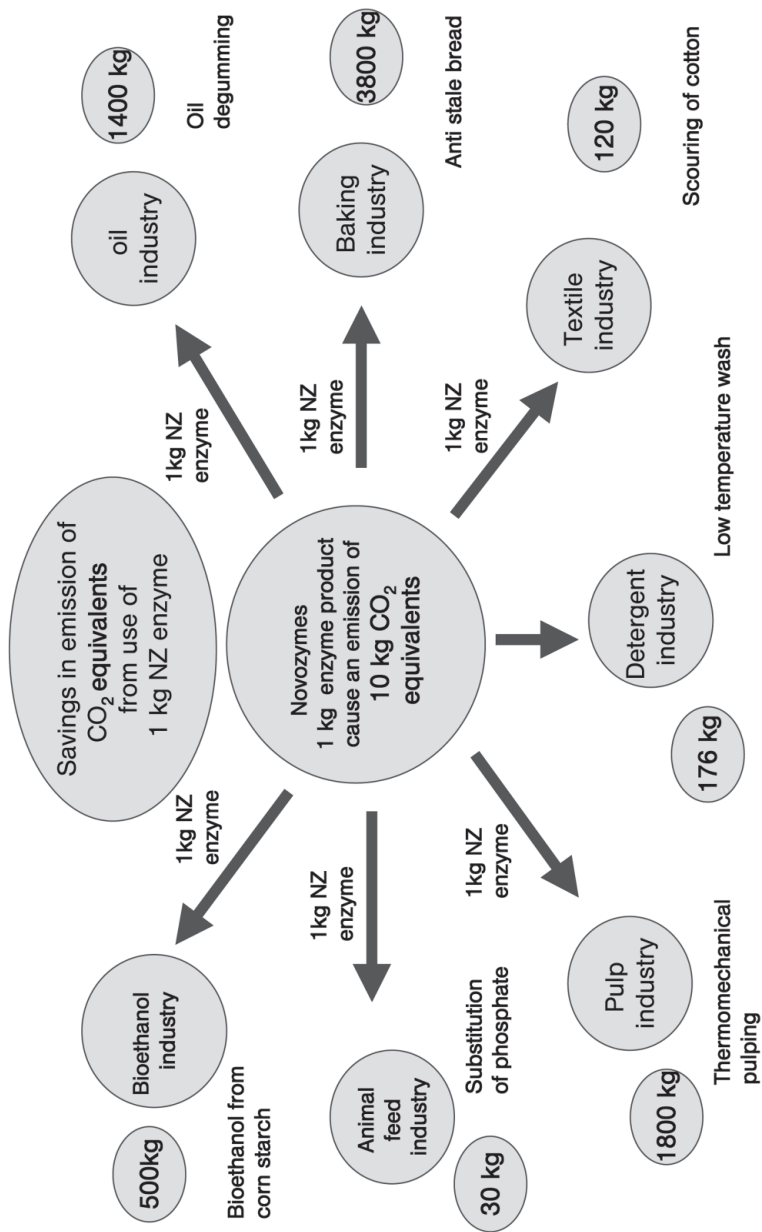


Figure 6.2 Potential impact of substituting chemical processes with enzymatic processes in different industries. Circles indicate the amount of CO₂ equivalents that is saved per kilogram of enzyme used.

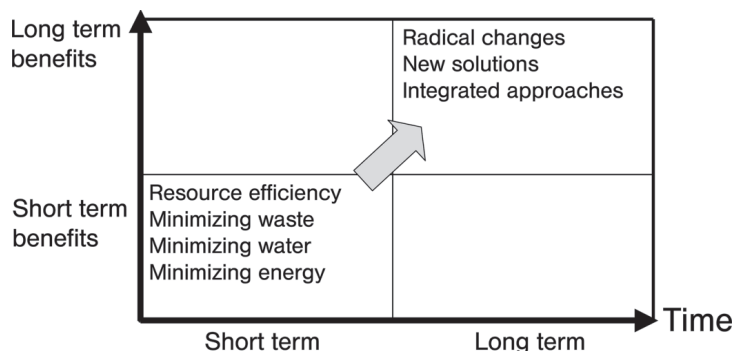


Figure 6.3 Eco-analysis of current and future biotechnological solutions for industrial processes. (Source: EU Chairmanship Workshop, 2004).

6.4 Biodiversity

The next topic is biodiversity: we tap the huge microbial biodiversity in Novozymes and our competitors do so too to develop pools of new enzymes. Our basic tenet is that whenever there is a suitable application of this technology, whenever we can identify the solution, we will be able to identify and develop the enzyme that is needed. This is what we have shown again and again. We have shown it for the very difficult task of degrading waste biomass and we feel absolutely convinced that we can do it for other tasks as well. This is based not only on Nature's diversity, but also on the new tools of gene shuffling and direct evolution that we can bring to bear in association with the biodiversity.

Not only can we do it, we can also do it quickly. The benchmark development time in our company now is 2 years, from when we first get the idea until we supply the first 100 tons of material to our customers. If we use pharmaceutical terms, it includes the discovery phase, the development phase and the approval phase, all of which can be done for a technical enzyme in 2 years. Not only can we do it quickly, we can also do it with very high yields and with very safe production organisms, because it is all standardized these days.

It can be concluded that we can actually use the technology and even incremental improvements help. The case is there for a very broad implementation over many different industries and it can be done much more deeply than it is done today. The case is also there for radical solutions, and the technology is ready for the implementation.

6.5 Implementation

There are a number of barriers that slow implementation at present. One is the approval time, and we can consider an example from Europe where the approval situation is the most difficult. Novozymes is certainly in favor of very straight regulations, as we believe that is the best way to address the concerns in society. Hence we are not talking about deregulation. What we need is a well-functioning system that is straight, not a system where, because of political worries, things are simply waiting between different offices for up to 4 years for simple approvals. Another aspect is that today environmental advantages are not a driver for implementation of new technology. Health is a much better driver and we have seen that only when health aspects are brought forward do we see rapid implementation.

The first example here is phytase, which is an enzyme that when introduced in agriculture reduces phosphate pollution by 30%. It took a long time for us to implement this enzyme. It is now well implemented in Europe and reasonably well in the USA, but in Europe implementation only happened because bone meal was banned for health reasons. Then the alternative was finally adopted. Financially, it was attractive already before meat and bone meal were banned, but it takes a lot of effort to pass the barrier of implementation. There is a lot of resistance in the system. If people already have something that works, then they do not really want a change, unless the economic benefit is really decisive. Hence for the kind of marginal benefits as in the case of phytase, 10–20%, it is not enough and something extra is needed such as a ban on meat and bone meal. The other example is bioethanol. This is an industry that is not on the move because of environmental benefits, but is simply because methyl tertiary-butyl ether (MTBE) is being phased out as a fuel additive for health reasons.

To go for the radical solutions, as already mentioned, we need to team up much more closely with other stakeholders in society. It is obvious that when it is so difficult for us to implement even incremental changes, then to go for the real radical solutions we need support from policy makers so that somehow we will point society in a specific direction, which is more sustainable. Then we might be able to change something.

6.6

Conclusion

The environment is not really a driver for policies and implementation of new technology, as we see it and as we experience it. For us really to make an impact, this will have to be the case tomorrow and for that we need support, especially from the EU. The reason I am focusing on the EU here is that the support in the USA is actually much better for these things. In the USA one often has a much more receptive policy-making situation than in the EU. It is hoped that matters will improve in the EU also, so that we can enlist the support of policy makers. We must make sure that the small incremental changes are implemented much faster than we see today so that we can also go for some of the radical solutions. One large area, of course, that is of concern in Europe is the reluctance among the European population to adopt these technologies and also there we need the support from politicians.

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Module III

New Energy Development

Introduction

Dominique Lecourt

Certain gases present in the atmosphere make it possible for our planet to profit from the greenhouse effect, which is a natural phenomenon essential to life. However, more recent demographic and economic developments have disrupted this fragile balance by injecting increasingly large quantities of carbon dioxide (CO₂), especially through the combustion of fossil fuels or by massive deforestation. These emissions exceed the capacity of ecosystems to “fix” this CO₂ – thus removing it from the atmosphere – and the atmospheric rate of CO₂ continues increasing. Using recent advances in molecular biology and genetics, can solutions be proposed to the predicted exhaustion of current energy resources, as well as contributing to progress in medicine? Through the influence of Craig Venter we are turning increasingly to the oceans for answers. He has created a revolutionary approach to understanding microbial metabolism. Consumption of fossil fuels in all economic sectors, from their use in buildings as well as in the whole of industry and transport, is the principal cause of CO₂ emission. Increased understanding of microbial metabolism can, for example, lead to new methods of blocking CO₂ emissions, as well as producing more and cleaner energy. Reduction of these emissions should be one of the major goals of the 21st century. Should technology become available now, and if the “biorefineries” bring about the advent of a “bio-based economy”, the question of how this development can be promoted must be addressed. This question is also economic and political, and takes on an additional – and critical – meaning in the context of developing countries: How can we prevent agricultural production intended for biofuels from competing with the imperative of feeding the population?

Author Biography

Jean-Jacques Bienaimé



*CEO, BioMarin Pharmaceutical; Former Chairman, CEO
and President, Genencor International*

Jean-Jacques Bienaimé has recently been named chief executive officer of BioMarin Pharmaceutical located in Novato, California. Prior to that he acted as Genencor International's chairman, chief executive officer and president. He joined Genencor in November, 2002 from SangStat Medical Corporation (NASDAQ: SANG) where he served as chairman, chief executive officer and president. Since 1998, he managed SangStat's growth from a \$4 million company to over \$100 million and guided the company to profitability. A biotechnology company focused on immunology, SangStat has two drugs on the market and two more in advanced stages of clinical development. Before joining SangStat, Jean-Jacques Bienaimé was senior vice president of corporate marketing and business development at Rhône-Poulenc Rorer Pharmaceuticals (now Aventis), a \$6 billion business, where he was responsible for worldwide marketing, medical affairs strategy, licensing and business development. Prior to that position, he was vice president and general manager of RPR's advanced therapeutic and oncology division. Other highlights of his career include five years at Genentech where he was director of marketing, Cardiopulmonary Products.

Jean-Jacques Bienaimé is a member of the board of directors of Aerogen Inc., NeurogesX and Saegis Pharmaceuticals. In June 2004, he was named to the Biotechnology Industry Organization (BIO) board of directors. Elected for a two-year term, he will represent the industrial and environmental section of the biotechnology community. He received an MBA from the Wharton School at the University of Pennsylvania and an undergraduate degree in economics from the Ecole Supérieure de Commerce de Paris.

7

How Can the Environment Benefit from Bioindustry Innovations?

Jean-Jacques Bienaimé

7.1

Introduction

This chapter provides an update on Genencor's vision and progress towards the biobased economy. Genencor is a profitable biotechnology company, with over \$400 million revenues in 2004 and a nearly 10% increase in product revenues, and we are basically using our strong financial, commercial and technical base to expand the boundaries of biotechnology and use that expertise to address significant problems such as the use of chemical and biological weapons and the ability to destroy prions that cause mad cow disease with prionase, for instance. We view ourselves as catalysts of the biobased economy through the development of novel biochemicals, bioenergy and biomaterials and also new nanotechnology products through a Silicon Biotechnology Alliance with Dow Corning.

We believe the industrial application of biotechnology will make overall industrial processes more sustainable and deliver to society a higher standard of living with a reduced environmental footprint. There is an obvious need for sustainable solutions and we are all aware of the need to do things differently and that biotechnology can really help do that. We can, for instance, reduce our dependence on fossil fuels and other non-renewable resources, we can reduce biodiversity depletion, reduce hazardous waste streams, reduce greenhouse gas emissions and basically turn over to future generations a world that can sustain them as well as it sustained us, if not better.

7.2

The Biobased Economy

There are several definitions of a biobased economy, but in Genencor's view it is basically an economy that uses renewable raw materials to produce products and energy, and such an economy in essence would reduce our dependence on fossil fuels, reduce energy consumption and reduce overall waste and pollution. There has been a number of recent studies that actually add credit to this vision. Recently the *Journal of Industrial Ecology*, which is a peer-reviewed journal that is published jointly by MIT and Yale, devoted a full issue to the biobased economy subject and the National Resource Defense Fund (NRDC), which is a US environmental group, has published a report supporting biorefineries (N. Greene, *Growing Energy – How Bio-fuels Can Help End America's Oil Dependence*, NRDC, 2004), which is something that will be developed here, and clearly the biobased economy is starting to catch the imagination of the media, the policy makers and the environmentalists.

In addition to developing basically biological routes to existing products, the biobased economy will also create new innovative products that cannot be produced today through petrochemical processes and there will be a range of industries whereby biotechnology will deliver industrial benefits again, such as novel biomaterials, bioenergy and fuels, novel chemicals and biopharmaceuticals, and, as is the reality today, we have more and more processes to manufacture pharmaceuticals that are biologicals instead of chemicals. There are also emerging personal care products at Genencor, and we are developing novel enzymes to be used in skin care and hair care and also in the emerging area of biosafety and biodefense. Together with the US Department of Defense we are starting to make available products to decontaminate, for instance, areas that have been contaminated with nerve gas such as the sarin gas that was used in the Tokyo subway terrorist incident in the 1990s.

7.3

Benefits of the Biobased Economy

The benefits of the biobased economy cover three dimensions: economic, environmental and social spheres (Figure 7.1). In the economic sphere, clearly the obvious benefit is that this biobased economy will reduce costs through improved production efficiencies and not only will biobased products compete with products that are currently made with oil, but there will also be innovative products such as Sorona[®] at DuPont, on which we are cooperating, that cannot otherwise be made with a petrochemical process.

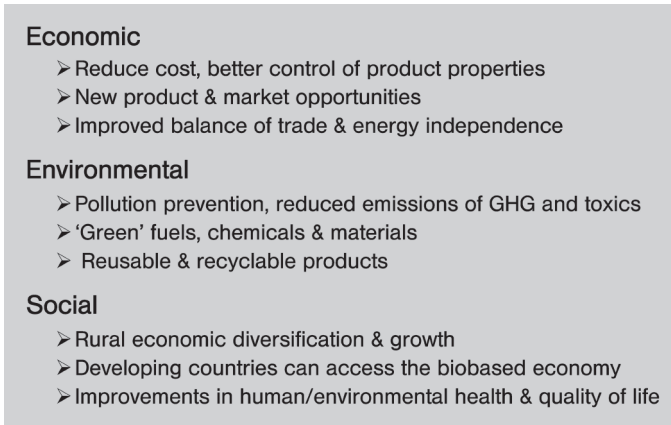


Figure 7.1 Benefits of the biobased economy.

In the environmental sphere, the OECD has reported on the importance of ecological efficiencies that are gained what one switches from a chemical process to a biological process, and finally in the social sphere the biobased economy will improve the economy of farmers, will reinvigorate rural economies and also allow developing countries that have no oil to use their renewable resources and their biomass to meet their industrial needs for the production of material wealth.

At Genencor, we have been working towards this for over 20 years. We have pioneered this vision and we are working with industrial leaders such as DuPont, Procter & Gamble and Cargill basically to replace chemical processes with bioprocesses. Genencor enzymes are found in a variety of products that are used every day, but the general public probably do not know about it. We sell over \$120 million worth of enzymes to Procter & Gamble, for instance, for detergents. Our enzymes are used for starch processing for sweeteners and soft drinks such as Pepsi-Cola and Coca-Cola, and if you live in the USA most of the time when you go to a gas station and you pump gas into your tank, 5–10% of it is actually not gasoline, it is ethanol, which very likely is manufactured through a process that uses Genencor enzymes. Also, recently, we have been working with Danisco, and have been introducing novel products to the market that add nutritional value to food, beverages and feedstock for animals.

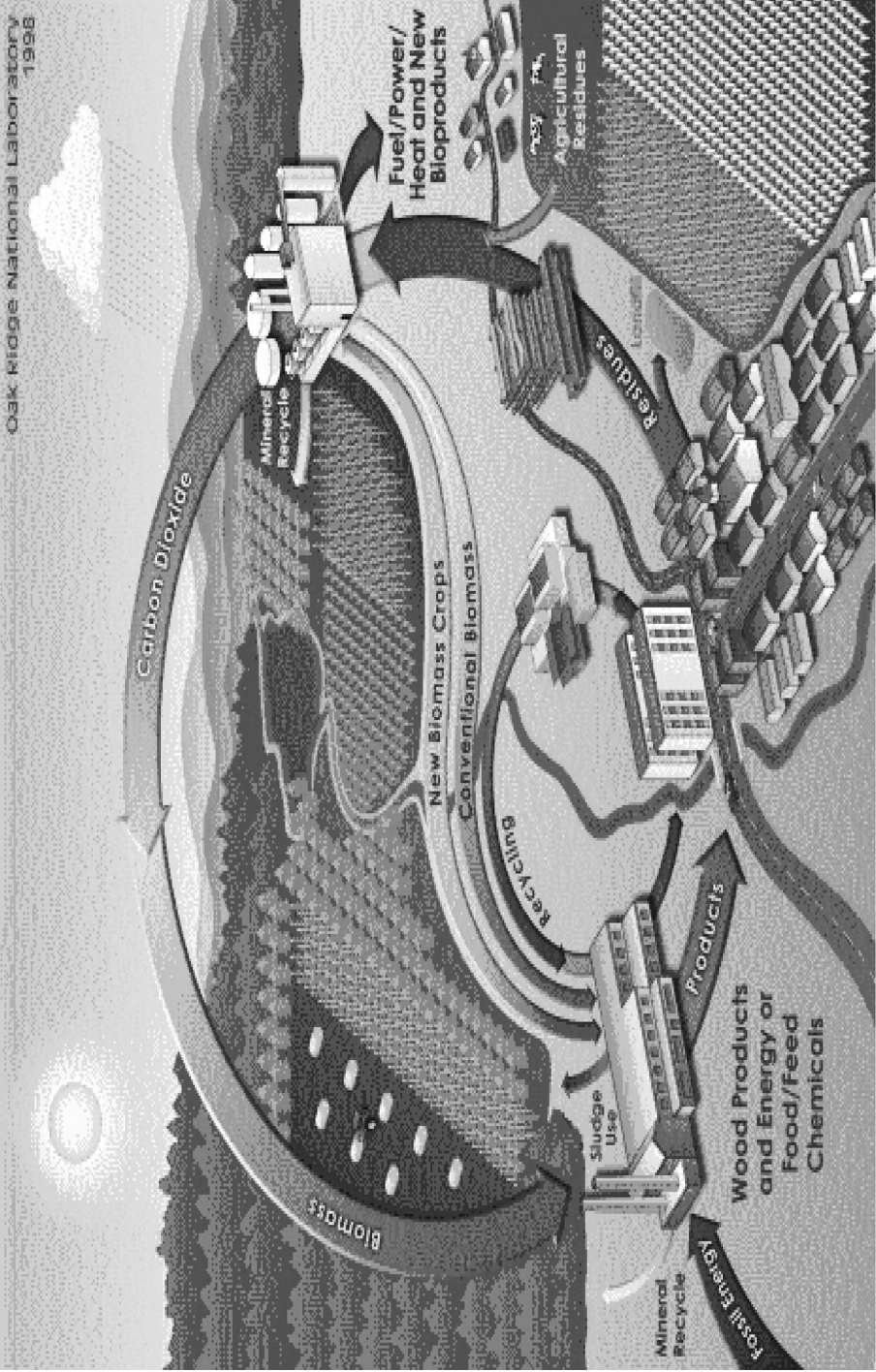


Figure 7.2 The biorefinery as seen by the Oak Ridge National Laboratory.

7.4 Development

We appear to be at the threshold of a new era, and Figure 7.2 is from the national renewable energy laboratory of the US Department of Energy. We believe that our enzymes will enable biorefineries to take their place alongside old refineries and other types of chemical-based manufacturing facilities. So in this biobased economy, the farmers will continue to produce grain for food and feed use, but the non-food parts of the food crops such as corn stover or wheat straw will be the raw material that fuels this new refinery and this refinery, like all refineries today, can make energy products, but it can also make products that are used in advanced economies such as bioplastics and novel polymers. In this ecosystem, the advantage is that the carbon is recycled. Basically the carbon that is consumed when these products are used is balanced by the fact that it was fixated in biomass, so there is a zero or near-zero net emission profile of greenhouse gases and clearly these refineries using our enzymes will produce multiple types of products using different enzymes and cell factories.

Figure 7.3 illustrates our image of the Genencor biorefinery. Clearly, these biorefineries will be driven by a range of products that Genencor has excelled

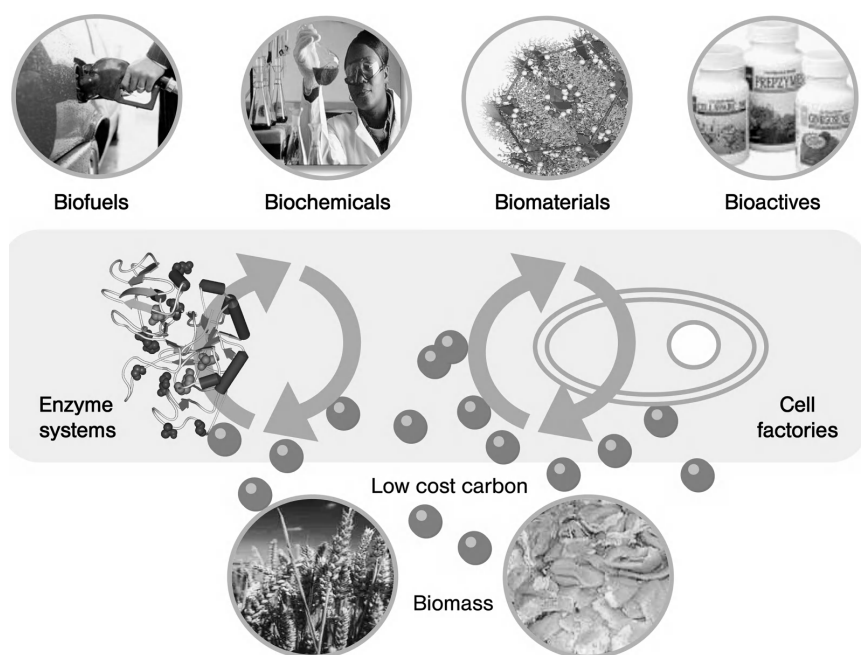


Figure 7.3 The Genencor concept for a biorefinery.

with, which are enzyme systems and cell factories. Through the enzyme systems and through cell factories, we will be able to break down the biomass and make fuels and potentially other products such as biomaterials, e.g. the new polymer that DuPont is launching called Sorona[®], which is made with modified microorganisms from Genencor.

7.5

Ethanol Production

Some statistics on ethanol production in the USA will be given because it has been growing very fast in the past few years. This is clearly connected with the increased price of oil and further increase in oil prices will likely result from the new demands from rapidly industrializing societies such as China. In 2004 there were 81 plants in 20 States in the USA producing 3.4 billion gallons of ethanol, which was an increase of 21% over 2003 and more than double that in 2000. At the end of 2004, there were 16 plants and two major expansions that were under construction, representing an additional 750 million gallons of production capacity. Basically in 2004 the US corn ethanol industry processed a record amount of almost 1.3 billion bushels of corn, which is a record 11% of the US corn crop. According to the US Department of Agriculture, the ethanol production increases the price that a farmer receives from corn by about 25–50 cents per bushel which reduces the need for government subsidies and in this respect Europe appears to be lagging behind.

Let us consider the economic impact of ethanol. In 2004, the production of biobased ethanol added \$25 billion to the gross domestic product, created 147 000 jobs, boosted household income in the USA by over \$4 billion and, which is always good for governments, added over \$1 billion of tax revenues to the Federal government and another \$1 billion to State and local governments. What is the environmental impact of ethanol in the USA? The 2004 production of ethanol reduced carbon dioxide equivalent emissions by ~7 million tons, which is the equivalent of the emissions that are generated by 1 million cars on the roads every year. Hence clearly in the biobased future we can continue to reduce carbon dioxide emissions. Actually, if all available biomass in the USA was used for the production of bioethanol, we could reduce CO₂ emissions by 1.7 billion tons, which is about 80% of the transportation sector's share of CO₂ emissions and 22% of all carbon dioxide emissions in 2002.

Of course, any responsible carbon reduction strategy must begin with ethanol, but it cannot end there – this is not the final solution. Even if we convert all biomass we still would need other sources of energy and the NRDC report envisions that we must integrate an ethanol production strategy with hybrid car technology and smart growth strategies in urban planning and

design and many other ways of developing an energy policy. The significance of the NRDC report cannot be understated. It was a three-way project that involved the NRDC, the US National Resource and Energy Laboratory (NREL) and Dartmouth University; it was a 2-year study, including among its contributors a long list of leading academic national laboratories and environmental experts, and it not only forecasts the potential for biomass ethanol, but also makes technology and policy recommendations as to how their vision should be achieved. The report provides fact-based analyses needed to force a coalition of farmers, environmentalists and technologists to advocate policies in support of the commercialization of this important technology.

7.6

Biomass Conversion

The biomass source needs two critical characteristics which it does not quite have today. It must be low cost – that is absolutely critical. Today most ethanol is produced from the edible part of corn, so it is not cheap enough. Second, it must have a low energy input profile, because if it requires a lot of energy to grow biomass, then to make energy from it is not really a very sustainable proposition. However, today we believe it is going to be achievable very soon because most of the US studies now assume a cost of biomass of \$30–40 per US dry ton of biomass, and this price is realistic if the chief material is from the waste stream such as corn stover or wheat straw, but this price can also be achieved with a dedicated energy crop such as switchgrass (*Panicum virgatum*), which requires little or no fertilizer or irrigation. Switchgrass is also called prairie grass and grows in most of the continental USA, and it is a favorite meal of ruminants such as the buffalo. No matter what the biomass source is, the greatest yield per acre with the lowest input per hectare is needed to achieve a sustainable agricultural system.

There is another key element, namely that the biomass cannot be transported for more than 50 miles, because if it is then again one is burning energy to create energy, which is uneconomic and is why the biobased economy will be closely linking farm economics with local economies. It has to be close to the farming community. Hence the main obstacle is to reduce the cost of biomass to create fermentable sugars. Currently, basically all bioethanol that is produced in the USA is made from the edible portion of crops, mainly corn, and government tax and subsidies are necessary to make it cost-effective compared with fossil fuels. If one can reduce the cost of sugars, clearly the biorefineries will become realities and biotechnology will enable us to convert, as shown in Figure 7.4, cellulose from plants into fermentable forms of sugars.

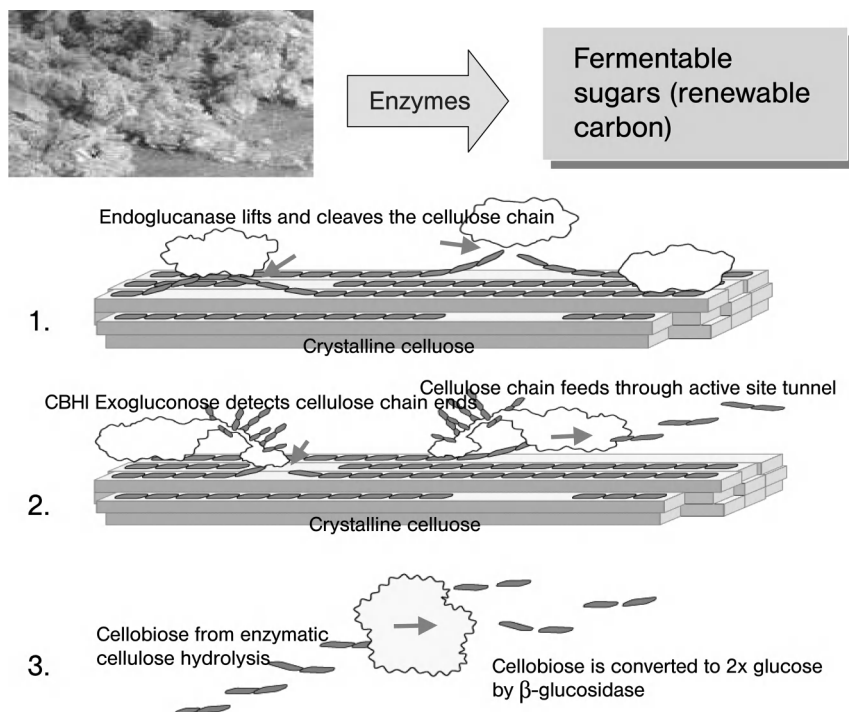


Figure 7.4 Converting cellulosic biomass to sugar using cellulase enzymes. Pretreated cellulose (top left) is converted to fermentable sugars by the action of several enzymes that break up the crystalline cellulose matrix.

Last year at Genencor, we concluded a 4-year research contract with the US Department of Energy and we exceeded the contract requirements because we were able to reduce the cost of the associated cellulase enzymes by over 30-fold. Therefore, it is now 30 times less expensive to make this enzyme than it was 4 years ago, and again this is key to making this technology cost-effective. We have developed an enzyme cocktail of several cellulase enzymes that break down the rigid crystalline structure of the cellulose polymer into glucose, which is a simple sugar that then can be fed to alcohol-producing yeast. This sounds relatively easy and straightforward, but is usually a huge technical challenge because basically one is fighting against millions of years of evolution that has been trying to make plants stand erect and every gardener knows how long it takes for grass clippings and organic waste to revert to humus.

It is not that easy to break down recalcitrant cellulose, but we are getting there and we believe that we are close to overcoming the technical challenge. Now the key challenge that is confronting commercial biorefineries is the technical integration of all the systems, the pretreatments, the cellulase enzyme

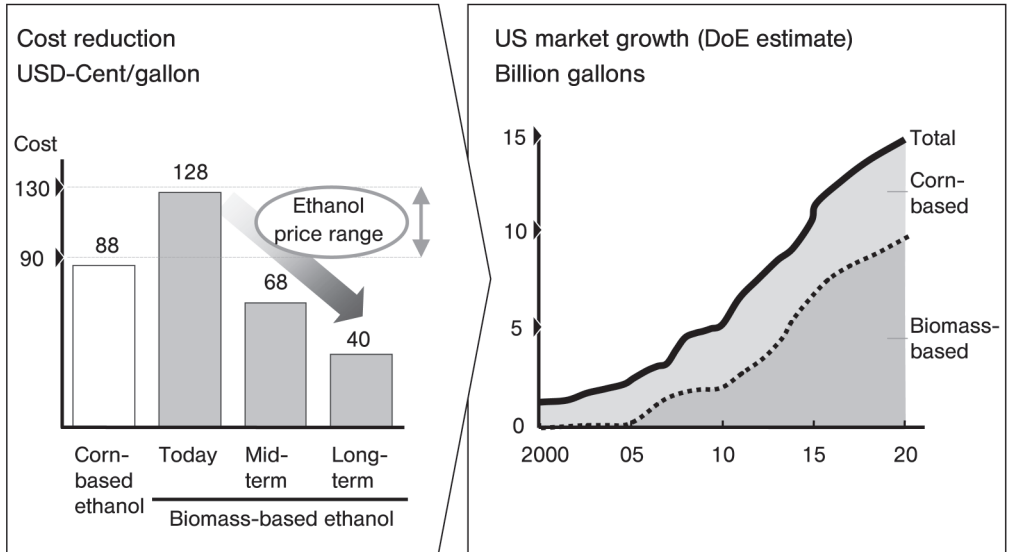


Figure 7.5 The bioethanol market in the USA. (Source: McKinsey & Company).

systems and the microorganisms to ferment the sugars. Also, clearly, the costs and the technical risk of these new fuel plants or manufacturing facilities exceed the rational investment parameters. The issue is that biomass ethanol must compete with fossil fuels that have had the advantages of over 100 years of progressive technical improvements in making oil refineries more and more effective and an integrated supply chain from the oil wells to the oil refinery to the gas station. We basically have to recreate a totally new system from scratch which is going to be very difficult without government help.

However, the future potential is huge. The data in Figure 7.5 were compiled by McKinsey & Company even before the price of crude oil exceeded \$50 per barrel. This rising oil price clearly will accelerate the development of ethanol production as there is a building boom for ethanol plants going on in USA, as indicated earlier. In the *Wall Street Journal* in March 2005 there was a front-page article that says that 25 new plants are under construction in the USA and many of them are owned by and operated by farmer cooperatives, i.e. farmer-owned companies. They are built by grass-roots investment syndicates who have recruited small investors in rural areas to participate in the ethanol boom. It is therefore an exciting time for the industry and it is building the infrastructure for the biomass to ethanol plants of the future. The current availability of crop residues in the USA that are basic crop wastes, which are not used today, is about 180 million tons per year. If all of it were converted to ethanol it would produce roughly 20 billion gallons per year or about six times what was produced in 2004. Hence there is still room for growth.

7.7

Policy Issues

Moving on to policy initiatives, the Biotechnology Industry Organization (BIO) has endorsed the NRDC reports and we are working with the US Congress to promote and enact some high-impact policies. BIO is lobbying for \$2.1 billion for R&D support over the next 10 years to develop biorefineries and integrate them. That is what is needed to overcome the technical hurdles that remain and mainly to finance the pilot plants to kick start the industry, and we are also supporting a production incentive package to provide funds and incentive to the early adopters of the technology. The EU ethanol industry is still in its infancy. I think that all of these policy principles should be considered in Brussels and the Member States should try to use this to achieve the biofuel directive targets and lay the groundwork for their own biobased economy.

Although we are making great progress in the USA, much has to be done to make biomass the economic driver in the equation. In the USA and throughout the world we need to invest in R&D, we need to fund the prominent policies that drive the development of the first billion gallons of cellulose-based biofuels and we need to adopt renewable fuel standards. There is an eco-requirement in the USA; most people do not know that 5% of all the cars that are manufactured in the USA today can actually work on 100% ethanol without any change to their engine – so if there were a really major oil crisis there would still be cars on the roads in the USA.

7.8

Conclusion

At Genencor we believe that biotechnology can contribute to fulfilling many of the unmet needs, both in human health and in industrial settings. We clearly envision a future where biotechnology helps to create a sustainable industrial system with a much reduced environmental footprint. The industry needs to articulate a vision of the future that society can embrace. We need to engage the public dialog in an open, transparent and modest way. We need progressive players openly engaged in building the future of the society that we envision.

Twenty years from now we will look back and we will see that biotech has contributed much more to human progress than just curing terrible diseases and I think we will be living then in a very flourishing biobased economy, and we at Genencor are looking forward to playing a very significant role in that.

Author Biography

Abel J.J. Rwendeire



Managing Director, Programme Development and Technical Cooperation Division, UNIDO

Leading the United Nations Industrial Development Organization's technical arm since September 2002, Abel Rwendeire is the Managing Director of the Programme Development and Technical Cooperation Division. In this capacity, his responsibilities cover the five main areas of UNIDO's core activities:

- Agro-industries and sectoral support
- Energy and cleaner production
- Industrial promotion and technology
- Multilateral environmental agreements
- Small and medium enterprises

With his appointment to UNIDO, Abel Rwendeire introduced a holistic approach to technical planning, which has resulted in a 20 per cent increase in project delivery. His formula for maximizing the impact of human and financial resources is based on fine-tuning and measurement of technical programmes from their conceptual stage through approval, funding and field coordination to implementation and long-term benefits. In so doing,

He has become the first UNIDO Managing Director to introduce an annual business plan that charts a comprehensive picture of where and when each technical activity is going each month.

Under his stewardship, projects backstopped by UNIDO's technical division have won awards for excellence from the World Chambers of Commerce, China's State Environmental Protection Agency, Egypt's Ministry of Environment and Yugoslavia's *Journal of Air Conditioning, Heating and Refrigeration*, as well as recognition for achievement from the United States Environmental Protection Agency and Guinea's Ministry of Fisheries and Aquaculture.

In striving to bring the benefits of industrialization to developing countries, Abel Rwendeire's latest initiative has been to create a facility in UNIDO for promoting emerging technologies – particularly in information and communications, hydrogen energy and genetic engineering – for the Organization's client countries.

For eight years prior to taking up his post with UNIDO, he served as Uganda's Minister of State for Industry and Trade as well as Member of Parliament. In this dual capacity, he spearheaded crucial initiatives for Uganda in trade capacity building, investment, exports, micro-financing, higher education and affirmative action for socially disadvantaged sections of the population. Between 1980 and 1992, he pursued a distinguished career as a senior academic in his country. He is the author of a number of books and articles both on development issues and on academic research and policy. After his undergraduate studies at Makerere University in Uganda, Abel Rwendeire earned his Ph. D. in Biochemistry at the University of Canterbury, New Zealand in 1985.

8

New Energy Development: Competing Priorities of Food Security and Biofuels

Abel J. J. Rwendeire

8.1

Introduction

Apart from the obvious issue of ensuring sustainable sources of energy, we definitely face also the question of preserving the environment and ensuring that greenhouse emissions are reduced. Currently 6.3 Gt of carbon dioxide are emitted into the atmosphere each year. Looking also at forests, 16.1 million Ha of forests are being cleared every year, mostly for wood fuel, but also for timber and other uses. If one considers the utilization of energy from biomass, only 11% of the energy is derived from biomass and if we consider electricity (Figure 8.1), the proportion of biomass is still smaller, only about 1.1% of the electricity being generated from biomass. Yet the whole account that we are looking at, as a society, is what energy is being used by the majority of the people in the world. If one looks at the global picture, the majority of the people in Africa and in southeast Asia use biomass and those who do not use electricity are almost the same as those who use biomass (Figure 8.2). This is a great strain on the environment, because the biomass energy that is used is not used efficiently. Hence there really is an urgent need to do something about the utilization of this energy.

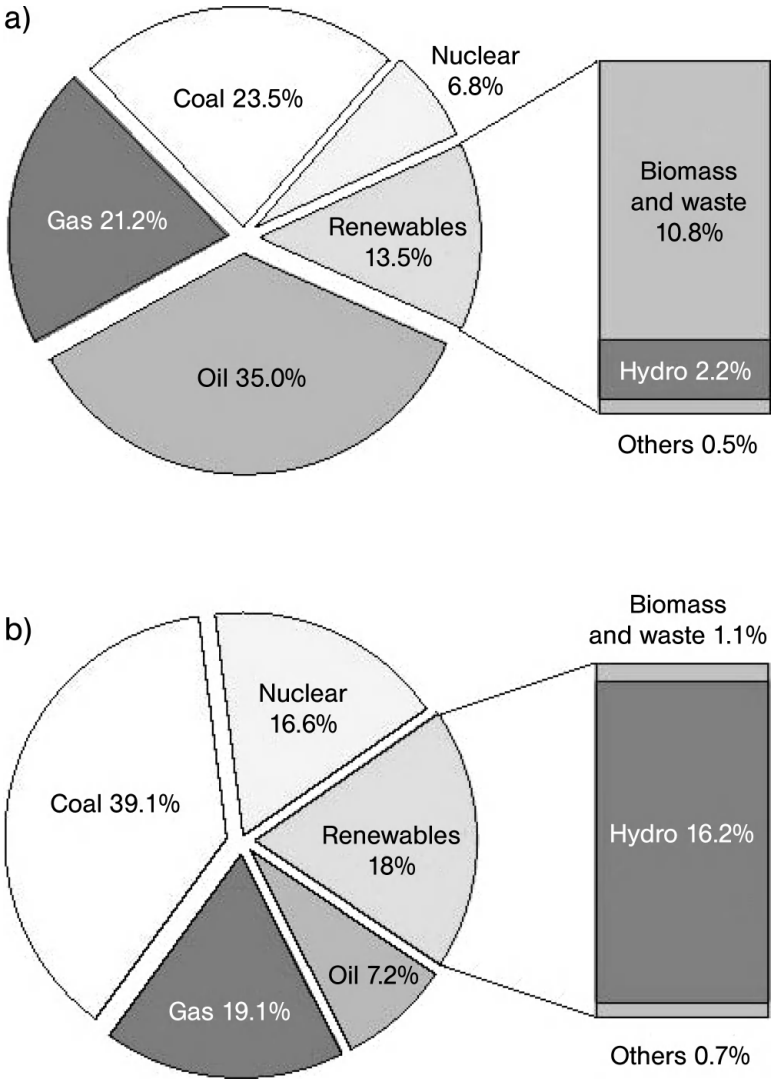


Figure 8.1 Contribution of biomass to world energy production.
(A) Share of biomass in world total primary energy supply as of 2002.
(B) Share of biomass in world electricity production as of 2002.
(Source: IEA Renewables Information, 2004).

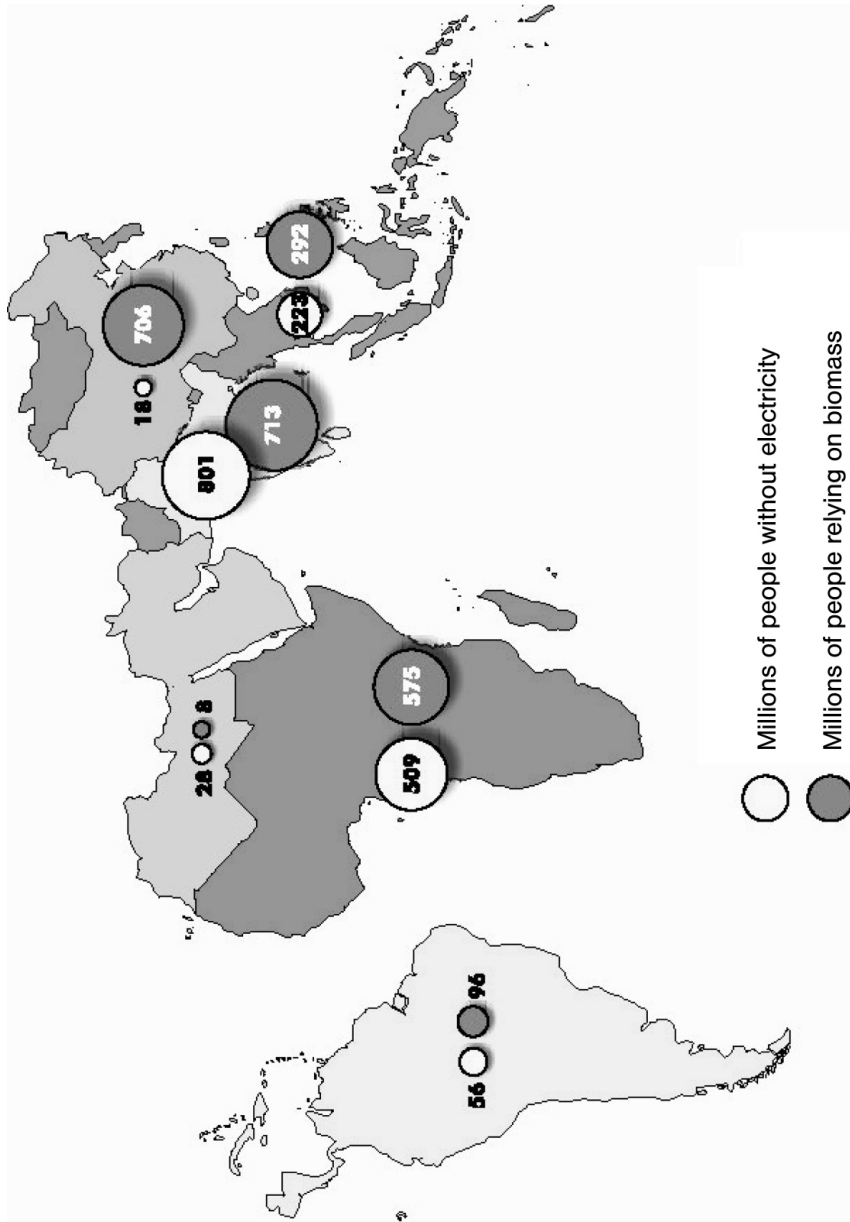


Figure 8.2 Global access to energy. The population without access to electricity (left) and those relying on biomass for their main energy needs (right) are shown for different parts of the world. (Source: IEA, 2002).

8.2

Energy Utilization

A study has been made of the utilization of electricity in relation to poverty and it turns out that there is a great deal of correlation between electricity use and the prevalence of poverty. If one looks at the countries that are predominantly poor, they also are predominantly utilizers of biomass and that biomass is utilized very inefficiently. For the developed countries, which use electricity, there is certainly less incidence of poverty so one sees in Figure 8.3 an impressive correlation between the utilization of energy and the incidence of poverty. Now, in most developing countries, certainly the utilization of biomass is very inefficient, using open fires for cooking and so on, which depletes the natural resources. Figure 8.4 from the Central African Republic shows the deforestation that is mainly due to charcoal making. In most urban areas in developing countries, and particularly in Africa, the electricity that may be available is not so dependable and also is expensive. Hence the utilization of charcoal is fairly high and there is a lot of deforestation. Hence although the rural community derives income from charcoal burning and selling, there is a great strain on the environment.

For agricultural production, even in the areas that would not ordinarily sustain very good production because there is a lack of irrigation, the land certainly is utilized and becomes almost unusable without replenishing either the minerals or the water. Hence inefficient long-term use of biomass certainly degrades the environment and also has negative effects on health, especially concerning smoke and lung cancer, and reduces agricultural productivity. Therefore, the economic benefits from the utilization of biomass must be balanced with the preservation of the environment and social needs.

In UNIDO, the way we look at the energy issue is to look at the climate change, the efficient utilization of energy in industry and the so-called clean technologies. The major part of our efforts actually concentrates on renewable energy, such as bioenergy, micro- and mini-hydrosystems, geothermal energy, and so on. The biomass that is utilized comprises wood residues followed by agricultural residues and then energy crops that are produced, but for all of these three categories, there are three major considerations (Figure 8.5). One is the quality of the material that is to be utilized. Even considering the enzymes that are used, some are easily obtained whereas others have to be produced through biotechnological processes that may be too demanding for developing countries that do not have such complex systems. The cost of the production of the materials and their collection is also important and finally the sustainability and land availability must be considered.

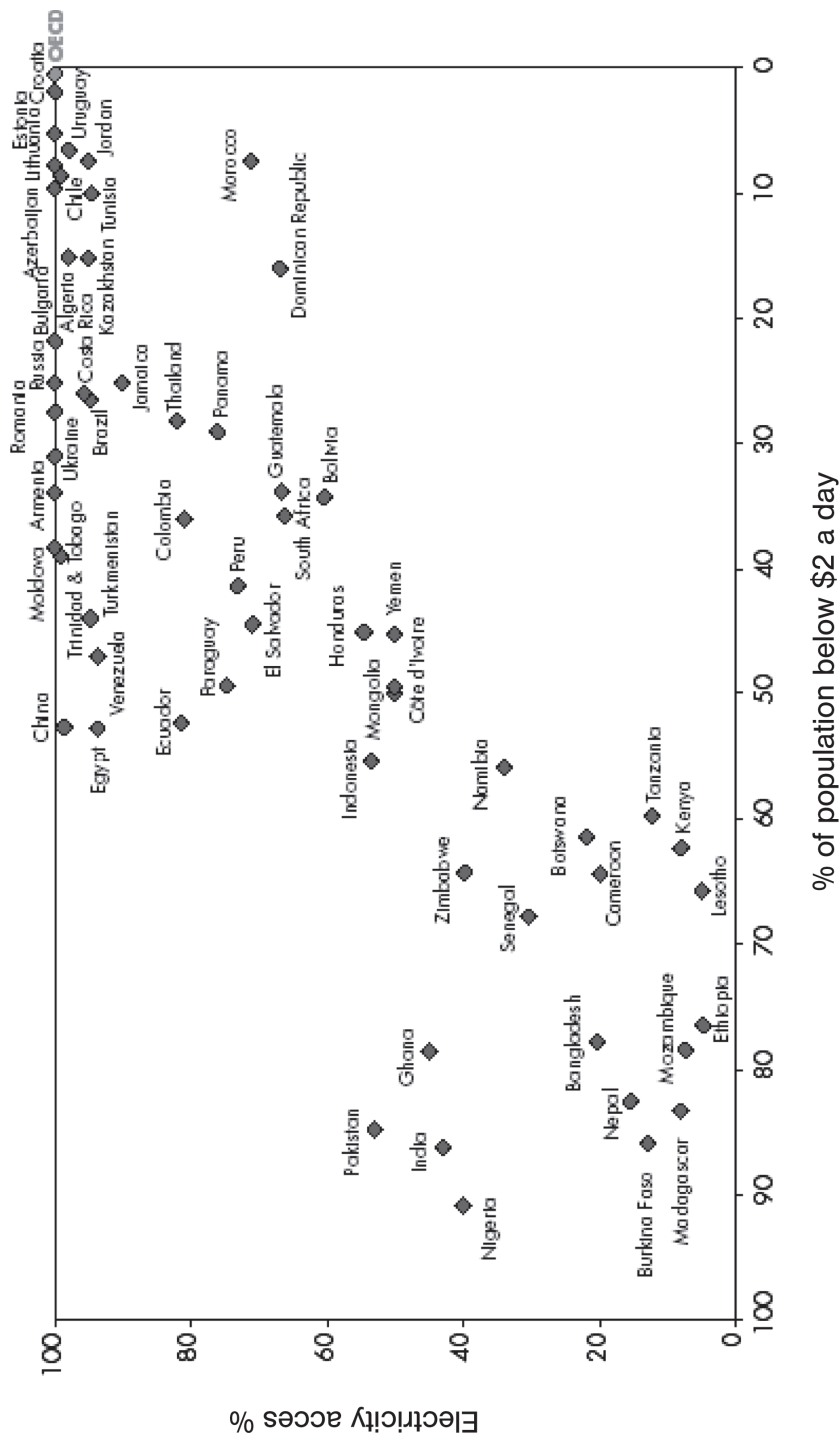


Figure 8.3 The link between poverty and access to electricity.
(Source: IEA, 2002 and World Bank, 2001).

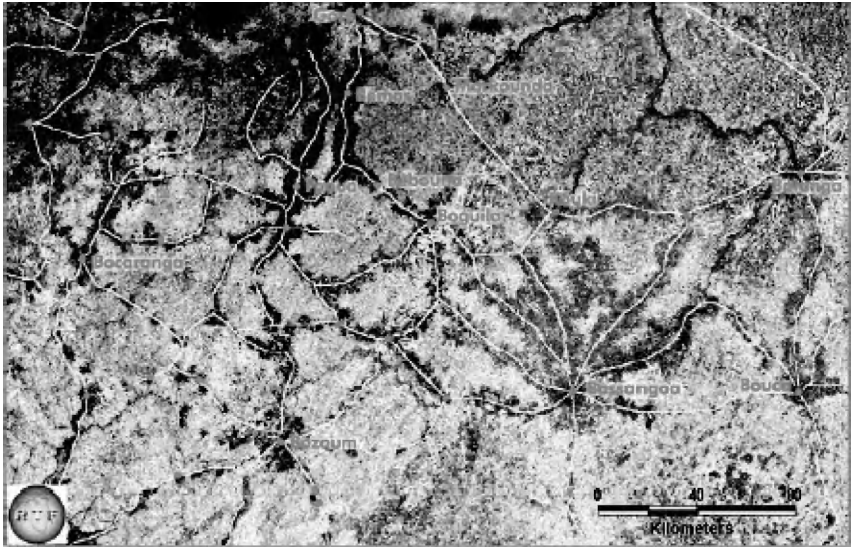


Figure 8.4 Charcoal deforestation in the Bangui area in the Central African Republic. The dark areas long the roads and tracks visible on this radar image indicate areas where forest has been cut to produce charcoal.

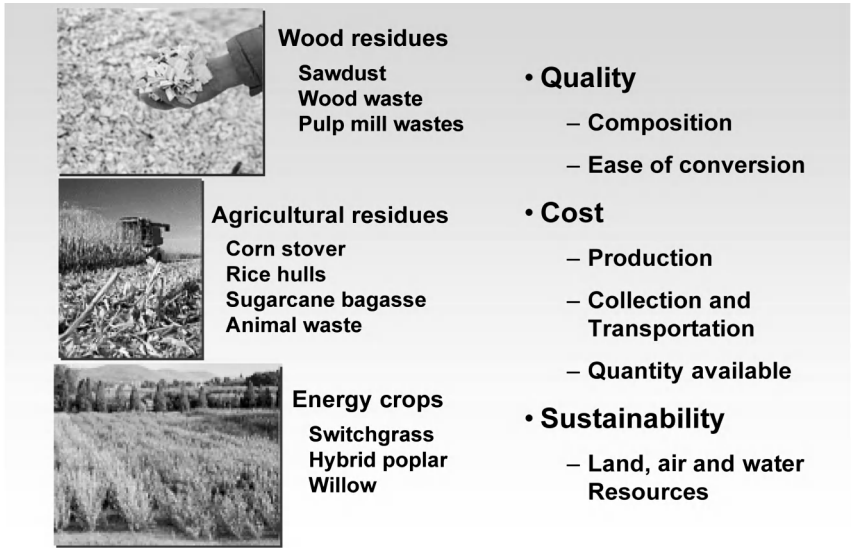


Figure 8.5 Key biomass resources and key issues in their utilization.

8.3 Biomass

The methods that are used in the generation of intermediates for biofuels are shown in Figure 8.6. Using enzymes, various materials can be degraded to produce intermediates for the production of either biodiesel or bioethanol. These require a lot of investment, as has been indicated by Jean-Jacques Bienaimé in Chapter 7. The issue of biodiesel and bioethanol is being looked at by many companies in the developed countries. It is emphasized here that producing this material that is meant for biodiesel competes with the production of foodstuffs. When we look at the benefits of biomass in terms of providing energy and also in terms of providing food, the least developed countries or developing countries would find it difficult to concentrate on the programs that would be focusing on bioenergy when their food security itself is a problem. Hence they would need to address food production first.

One of the main issues in developing countries is that the biomass is dispersed and so its collection is a costly factor. The second issue that is of concern is the type of technology for converting the biomass, and also there is the issue of scale. As has already been mentioned by Jean-Jacques Bienaimé in Chapter 7, to produce billions of gallons of ethanol requires a lot of investment in biorefineries and this kind of money may be difficult to find, certainly for developing countries. Hence for these countries, using biomass as an alternative source of energy becomes less attractive.

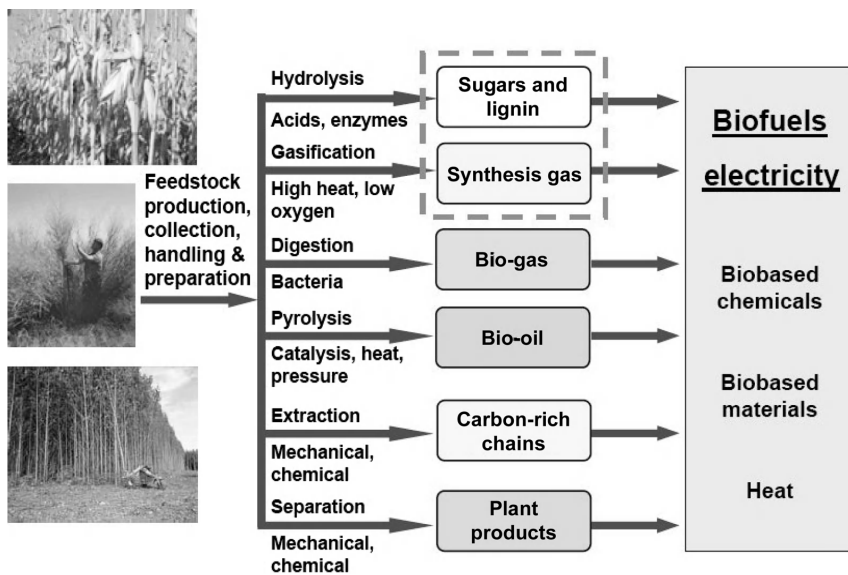


Figure 8.6 Current technologies used for converting biomass into energies.

The issue of biotransformation competing with the land available for food crops is illustrated by a report that was made by the UK Department of Transport. In a 2003 report, they looked at the production of producing biodiesel from rapeseed and some of the statistics are very interesting. One ton of the rapeseed would produce 415 kg of biodiesel and 1 Ha produces ~1.5 tons of biodiesel. Now, if one wanted to utilize biodiesel alone for fuel consumption, one would require to utilize 25.9 million Ha of land in order to produce enough biodiesel to satisfy the consumption of fuel in the UK. If we put the target only at the 20% quota that the EU requires its Member States to have changed to renewable energy, the UK would have to utilize 5.18 million Ha, which is almost all the available arable land, 5.70 million Ha, in order to produce enough biodiesel. Certainly if the UK cannot afford to utilize all the land it has for biodiesel production, one can definitely expect most developing countries to shy away from this prospect.

The issue of shifting from the use of fossil fuel does not mean that we should not now be looking at the efficient use of fossil fuels and certainly a lot of research is being carried out to ensure that the recovery of the oil is more efficient, for example through the utilization of biosurfactants. These are chemicals produced by certain specialized bacteria that ensure efficient extraction of the oil. Also polymers are used, especially xanthans from the bacterium *Xanthomonas campestris* that create a huge polymer blanket within the oil-containing formation that helps to direct the oil into the wells and extract it more efficiently. Also, using repressurization methodologies, one can increase the yields. Hence it is not only a matter of having the options of bioenergy, but also assuring that the extraction of the present limited resources is done efficiently (Figure 8.7).

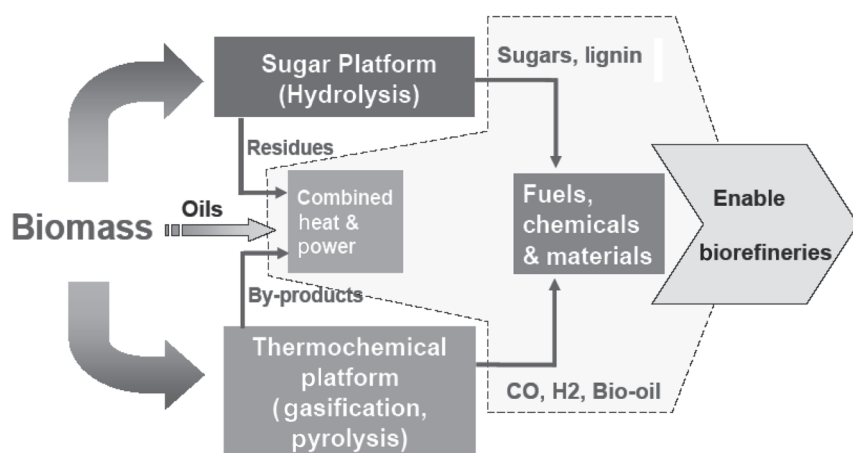


Figure 8.7 An integrated “conversion platform” for the industrial use of biomass.

For the least developed countries, as mentioned earlier, the issue of food security is uppermost and so there is less emphasis now on looking at bioenergy. The other challenge is to ensure that deforestation and desertification are stemmed and also to ensure that those technologies which are employed are used efficiently. Finally, they need investment and awareness to diversify energy production.

8.4

Alternative Sources of Energy

UNIDO focuses on the technology that is used and particularly on alternative sources of energy, among others looking at bioreactors, mini-hydrosystems and solar and wind energy.

The way in which UNIDO has been doing mini-hydro projects (Figure 8.8) is to ensure that there is capacity within the developing countries to produce or fabricate some of the equipment that may not be easily obtained by importation and also to ensure that once these plants have been installed, they can be maintained. Solar energy (Figure 8.9) is being looked at, but one of the major hindrances is that the cost of the cells is high and for rural transformation, certainly, this has not come out as a very attractive method, but UNIDO certainly will continue to look at it.

Tapping wind energy (Figure 8.10) is also one of the options that is being looked at, but again the costs of installing the structures and ensuring that the generation of energy or electricity covers a great deal of the rural sector are high. To improve the utilization of wood fuel requires at least the immediate solution of improved stoves and so we have been looking at installing improved stoves for domestic utilization (Figure 8.11). Another approach is the use of biogas digesters and this has been a popular program particularly in countries where biomass is easily obtained from both human domestic waste and animal dung (Figure 8.12). Biogas can easily be harnessed for domestic utilization, and also for small- and medium-sized enterprise utilization.

Another element that we have been looking at is gasification (Figure 8.13), utilizing some of the biomass materials to produce gas, which is then burned for the generation of electricity. This technology has proved attractive for certain countries and India is well advanced in utilizing this approach. If the raw materials are not too far away from the gasification plant, certainly there is a lot that can be done.

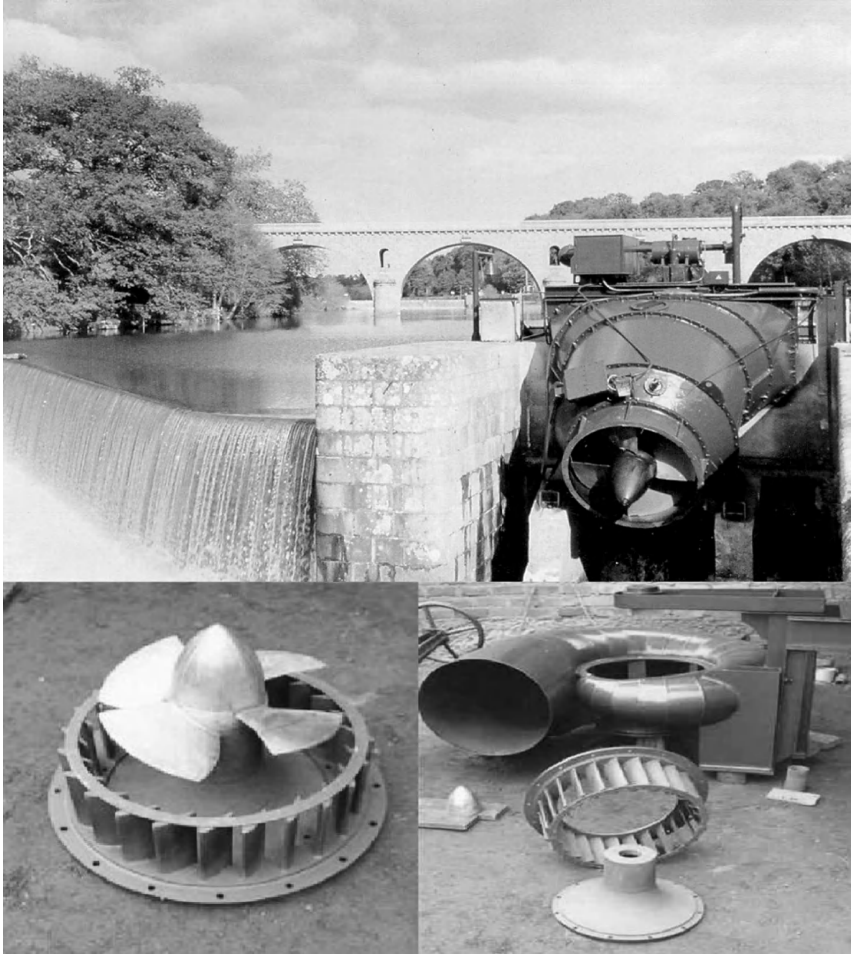


Figure 8.8 Small-scale hydroenergy plants (mini-hydros).



Figure 8.9 Solar energy for use in rural communities.



Figure 8.10 Use of wind energy to generate electricity in Indonesia.



Figure 8.11 Improved cooking stoves consuming less fuel and generating less toxic smoke.



Figure 8.12 Biogas digester as widely used in India.



Figure 8.13 Gasification plant in India.

8.5

Conclusion

To come back to the efficient utilization of these materials in developing countries, certainly one requires technology, skills and so on, and that means we would have to ensure that there is a forum that would look at a number of issues. UNIDO proposes the establishment of an International Forum on Industrial Biotechnology (IFIB), but really focusing on renewable sources and particularly bioenergy. This would be a multi-stakeholder forum comprised of the private sector, the policy makers, technical assistance agencies and civil society. The role of this body would be to look at the technologies and what these technologies imply or mean in terms of the economic development of the countries concerned, and further to look at the technology transfer, technology diffusion and technology management and to study technology alliances. Some of these technologies certainly are patented and ways of looking at the patent issues deserve considerable attention, and of course facilitating the implementation of regulations is also important.

With all of the above we would definitely be able to utilize bioenergy not only for developed countries but also for developing countries.

Author Biography

J. Craig Venter



The J. Craig Venter Institute; Former President and Founder, Celera Genomics

J. Craig Venter, Ph. D. is one of the leading scientists of the 21st century for his visionary contributions in genomic research. He is founder and president of the J. Craig Venter Institute and the J. Craig Venter Science Foundation.

The Venter Institute conducts basic research that advances the science of genomics; specializes in high volume genome sequencing, and explores the ethical and policy implications of genomic discoveries and advances. The J. Craig Venter Science Foundation supports both the Venter Institute and the Institute for Genomic Research (TIGR), and affiliated research organisation led by Claire M. Fraiser, Ph. D. Venter founded TIGR in 1992.

Education and Academic Affiliations

Venter earned his Bachelor of Arts in Biochemistry and a Ph. D. in Physiology and Pharmacology, both from the University of California at San Diego. He was Professor at the State University of New York at Buffalo and the Roswell Park Cancer Institute, before moving to the National Institutes of Health.

Key Accomplishments

While on faculty at the National Institutes of Health, J. Craig Venter developed expressed sequence tags or EST's, a revolutionary new strategy for discovering genes. In 1992, he founded the Institute for Genomic Research (TIGR). There, he and his team decoded the genome of the first free-living organism, the bacterium *Haemophilus influenzae*, pioneering the new whole genome shotgun technique. In 1998, he became the first president of Celera Genomics to sequence the human genome using the whole genome shotgun technique, new mathematical algorithms, and new automated DNA sequencing machines.

The completed sequence of the human genome was published in February 2001 in the journal, *Science*. In addition to the human genome, J. Craig Venter and his team at Celera sequenced the fruit fly, mouse and rat genomes.

In 2003, he launched a global expedition to obtain and study microbes from environments ranging from the world's oceans to urban centers. This mission, now in progress, is yielding insights into genes that make up the vast realm of microbial life.

Research Interests

Research at the Venter Institute reflects J. Craig Venter's interests in advancing the science of genomics and in applying genomics advances to some of the world's most vexing public health and environment challenges. Major research foci include human genomic medicine, environmental and evolutionary genomics (which includes the Venter Institute Global Sampling Mission), biological energy production, synthetic biology, and the intersection between genomics and environmental and energy policy.

Publication and Honors

Venter is the author of more than 200 research articles. He has recently published several papers on his scientific findings. The characterization of the genes from the Sargasso Sea appeared in the journal *Science* in March 2004. In December 2003, J. Craig Venter and colleagues published their research on a synthetic genome known as synthetic phiX 174. That paper appeared in the *Proceeding of the National Academy of Science*. In addition, he has received numerous honorary degrees and scientific awards including the 2002 Gairdner Foundation International Award and the 2001 Paul Ehrlich Award and the Ludwig Darmstaedter Prize. He is member of numerous prestigious scientific organizations including the National Academy of Sciences and the American Academy of Arts and Sciences.

9

Environmental Genomics

J. Craig Venter

9.1

Introduction

This chapter on environmental genomics builds on our early work on sequencing genomes. It has been not quite 10 years since we published the first genome of a free living organism, so if we look at all of the things that have happened in the last decade it turns out to be pretty remarkable. After we sequenced the first genome, we went on to sequence most key human pathogens, then on to plants, insects, animals, human, mouse, dog, rat, rhesus monkey and others. However, here we consider primarily the microbial world.

9.2

Initial Studies

We started with the microbial genomes and while sequencing the human genome we realized we had tools that could characterize the environment in a way that had not been done before. Microbes are part of the invisible world, but they make up at least half of the earth's biomass. The Archaea alone have more biomass than everything one sees in the visible world of plants and animals. For example, each milliliter of seawater has around one million bacteria and over 10 million viruses.

Some of the motivation for our initial studies was derived from the fact that we are dumping 3.5 billion tons of CO₂ into the atmosphere each year. This comes primarily from fossil fuels, but also from deforestation. The oceans are the largest carbon sink. Chemists thought they understood it but basically none of the biology in the ocean was understood and we decided we could try to understand this better by shotgun sequencing the ocean. We started the Sorcerer II expedition (Figure 9.1) in 2003 with some preliminary experiments



Figure 9.1 The Sorcerer II vessel making its round-the-world voyage.

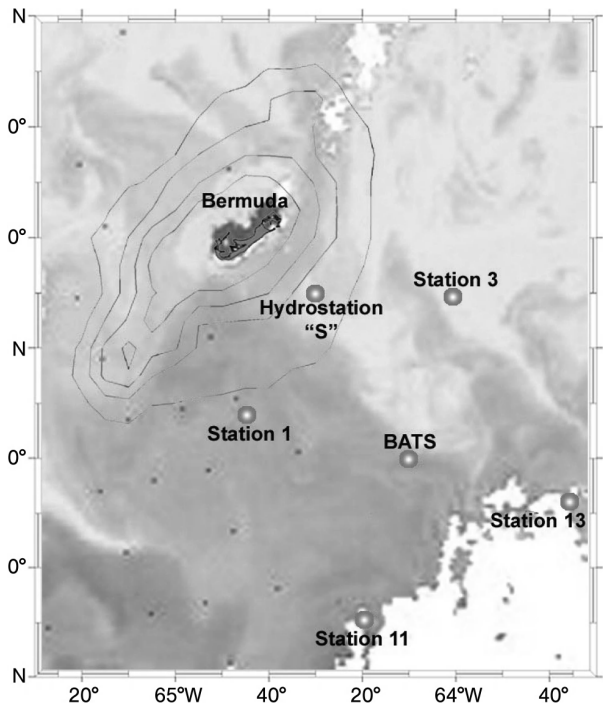


Figure 9.2 Sampling sites off Bermuda island. Different shades in this satellite image indicate different abundances of photosynthetic pigments in the waters around the island.

in the Sargasso Sea off Bermuda. We chose the Sargasso Sea because it was supposed to be a desert, low in nutrients, and therefore presumably limited numbers of life forms. However, satellite photographs like Figure 9.2, taken on one of the days of sampling, show that the oceans, even small areas, are not homogeneous and the data are now showing that on a global scale also.

9.3

Sampling the Ocean

Our protocols to fractionate the sea water samples are fairly straightforward. We have prefiltration followed by a 3 μm filter followed by a 0.8 μm filter, followed by a 0.1 μm filter, and everything that passes through that is collected on a 50 kDa tangential flow filter that traps the viral particles. Most of the bacteria collect on the 0.1 μm filter. We do get occasional small, single-cell eukaryotes, most of which show up on the 0.8 and 3.0 μm filters. It takes a few hours to filter the samples, depending on their diversity, then the filter is stored in a freezer and shipped back periodically to Rockville to our DNA sequencing laboratory (Figure 9.3), where we sequence over 100 million letters of genetic code every 24 h. This is a largely automated facility with 50 people who do all the sequencing and it is the same facility that is sequencing rhesus monkey, bacteria and the environment.

Amongst all the discoveries that came out of our pilot study that was published in *Science* (J. C. Venter et al., *Science* 304, 66–74, 2004), the most exciting one was probably all the new photoreceptors that were discovered. The sequences at the bottom of Figure 9.4 represented our prior knowledge



Figure 9.3 The DNA sequencing facility in Rockville, Maryland.

of photobiology, including the human visual pigments that we use for our own visual acuity. There were one or two bacterial rhodopsins known, but all the proteorhodopsins shown represent over 800 new ones discovered in the Sargasso Sea, and these discoveries have continued and we now have thousands of them. The abundance of photoreceptors suggests that essentially every organism in the upper parts of the oceans deals with photobiology. The tremendous diversity that we found here of tens of thousands of organisms went against what was expected from the low nutrient content. The photoreceptors grabbing energy directly from sunlight explain how we can have such tremendous biodiversity in an area lacking nutrients.

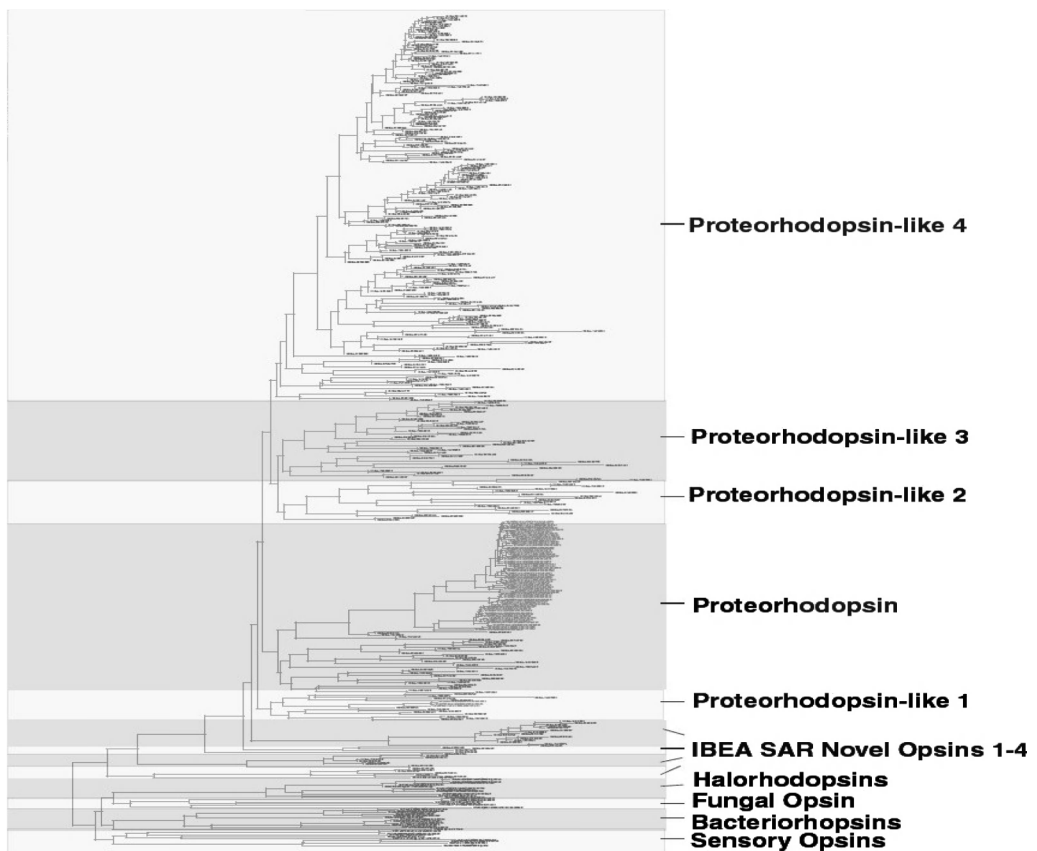


Figure 9.4 Phylogenetic tree showing all known photoreceptor protein sequences. The majority of these was found in the seawater samples collected at Bermuda island.
(Adapted from Venter et al., *Science* 304, 66–74, 2004).

9.4

Sorcerer II Expedition

The Sorcerer II expedition started in Halifax and we worked our way down the US east coast to the Caribbean Sea, the Panama Canal, Cocos Island and then down to the Galapagos (Figure 9.5), collecting seawater samples along the way. We also collected soil samples on various islands. Cocos Island off Costa Rica is the largest island on Earth uninhabited by people. There is a small ranger station there with some of the greatest biodiversity and that biodiversity is totally due to microbes. This island sits where the shelf drops off very quickly by thousands of meters. The currents that run up and down

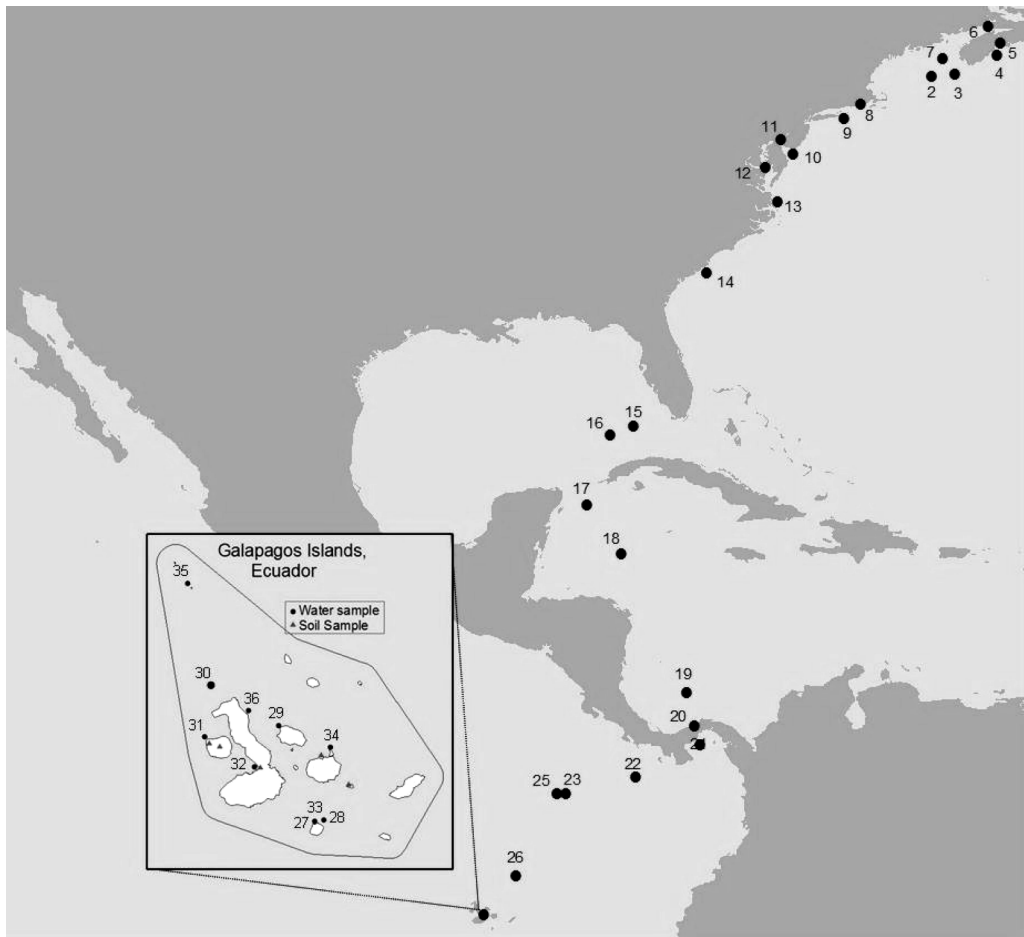


Figure 9.5 Sampling sites along the first leg of the expedition, from Halifax to the Galapagos archipelago.

central and South America hit this island, and there is a tremendous upwelling of deep bacteria that come up to the surface and drive the entire food chain. It is also known as the island of the sharks: schools of hundreds of thousands of hammerhead sharks migrate there, and also whale sharks.

We went down to the Galapagos where we had access to totally unique environments into which tourists are not allowed. When Darwin was there in the 19th century, he could pick up only the things that he saw, so he did experiments with the marine iguanas that inhabit the islands, but he missed all the millions of species floating around them.

The Galapagos are very hot and dry. The soil temperature there was on the order of 60 °C, giving us totally unique microbial populations. When species die, they basically become mummified instead of totally digested. One of the most interesting sites we characterized was what we called the flamingo pond on Floreana Island. It is relatively shallow and hot, over 40 °C. The salinity is three times that of the surrounding ocean. The water is very turbid and, as any microbiologist knows, this indicates that we are looking at saturated cultures of bacteria. There are also some brine shrimp in it. The brine shrimp feed off the bacteria and the flamingoes feed off of the brine shrimp. When we characterized this, it came out very different to what ecologists would have predicted. They said that there would be a small number of highly abundant species. Instead, we found clouds of related species (Figure 9.6) and I think that is starting to be the picture we are seeing in the environment as a whole, and so from the simplistic view from characterizing and culturing one organism we have clouds of maybe thousands of related organisms. After the eight clouds of organisms shown had been characterized, still over 75% of the sequences had not been assigned, showing tremendous diversity even in simple environments.

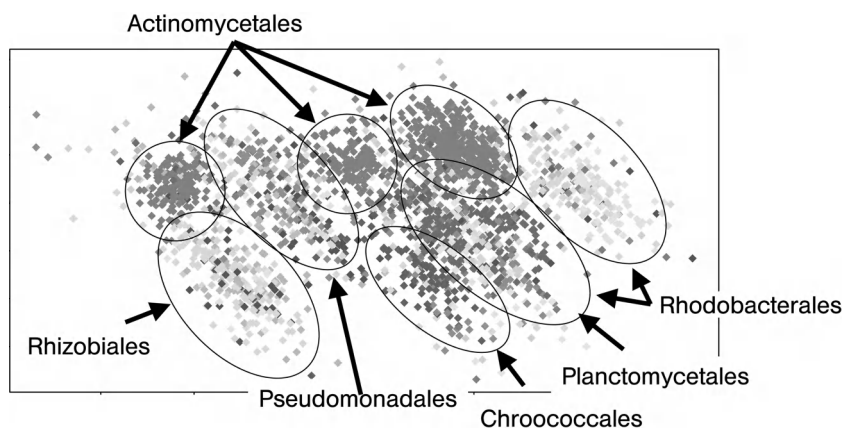


Figure 9.6 Microbial diversity in the sample taken from the hypersaline Flamingo pond on Floreana island. The taxonomy is based on dinucleotide frequencies.

Roca Redonda is one of the few places on Earth where warm seeps are accessible, and 60 ft below the surface there is hot sulfur gas bubbling out of the floor. Taking samples there was reminiscent of 1996, when we sequenced the first Archaea, only we had to go much deeper than using the Alvin craft to reach the high-temperature vent shown in Figure 9.7A. The temperature in the center of that dark cloud is 400 °C, whereas the surrounding water is at only 2 °C. The arrow points to where a piece of the chimney was broken off and taken back to Woods Hole, where a previously uncharacterized species of Archaeobacterium was cultured. *Methanococcus jannaschii* (Figure 9.7B) is an autotrophic Archaeobacterium that converts carbon dioxide into protein; in fact that is how it fixes carbon. It also makes methane and its energy source is hydrogen. It does not use sugar and it does not need any external sources of anything except basic elements. It is frozen at human body temperature, comes to life at 60 °C, its optimum temperature is 85 °C and it is happy in boiling water temperatures.

A preliminary analysis of the samples taken from Halifax to the Galapagos now adds at least 6.5 million sequences to what we found in the Sargasso Sea,

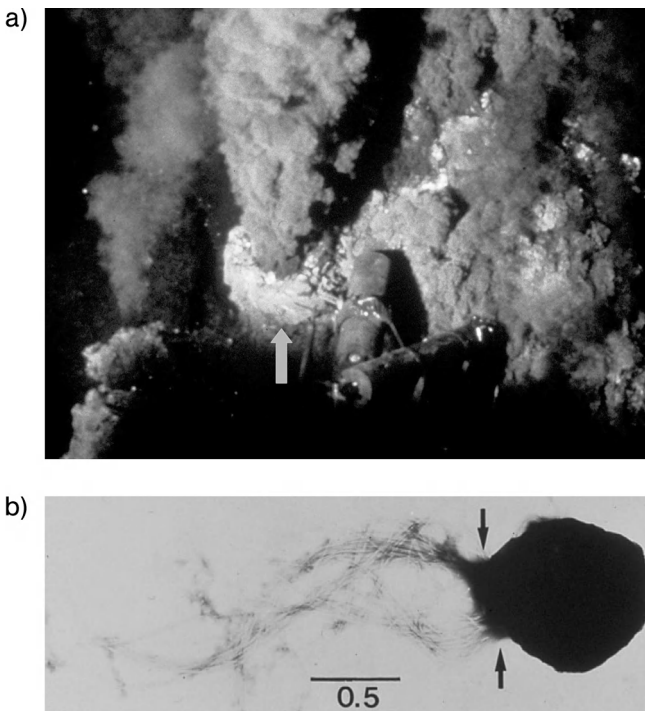


Figure 9.7 Hydrothermal vent (A) from which the Archaeobacterium *Methanococcus jannaschii* (B) was retrieved, the first Archaeobacterium to have its entire genome sequenced in 1996. For details, see text.

and this represents just preliminary data based on the analysis of 59 million reads. It includes over 10 000 distinct organisms, and that is the minimum estimate. The site off Bermuda yielded on the order of 47 000 new genomes. Therefore, we estimate that each sample every 200 miles yields somewhere between 40 000 and 50 000 species, 3.8 million genes with some similarity to the known world and 2.7 million that do not match anything. One of the most amazing statistics is that 85% of the sequences are unique at every site around the globe that we have sampled thus far, and less than 10% of the data is part of large assemblies at one site or across sites. Of the 10% of sequences from those assemblies, 3% come from multiple sites and therefore are interesting in terms of global distribution. We grouped the data according to the water temperatures of the sampling sites and found a very distinct distribution between the cold samples and the warm samples (Figure 9.8). There is a lot of differential information amongst the warm samples, but the situation is clear-cut just between cold and warm water with the assembled species.

We now have on the order of 3000 photoreceptors, so, we have to line up thousands of proteins. There is a three amino acid sequence that tells us the wavelength of light that these photoreceptors interact with and we were stunned when they were in an unusual distribution of the sites down the coast and through to the Galapagos (Figure 9.9). A brief summary is as follows.

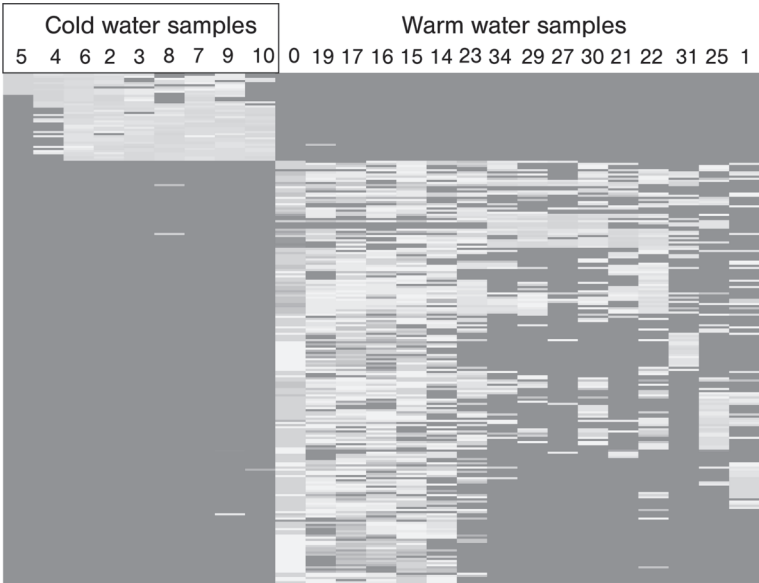


Figure 9.8 Comparison of significant scaffolds between cold water samples (left) and warm water samples (right) yields a distinct clustering pattern.

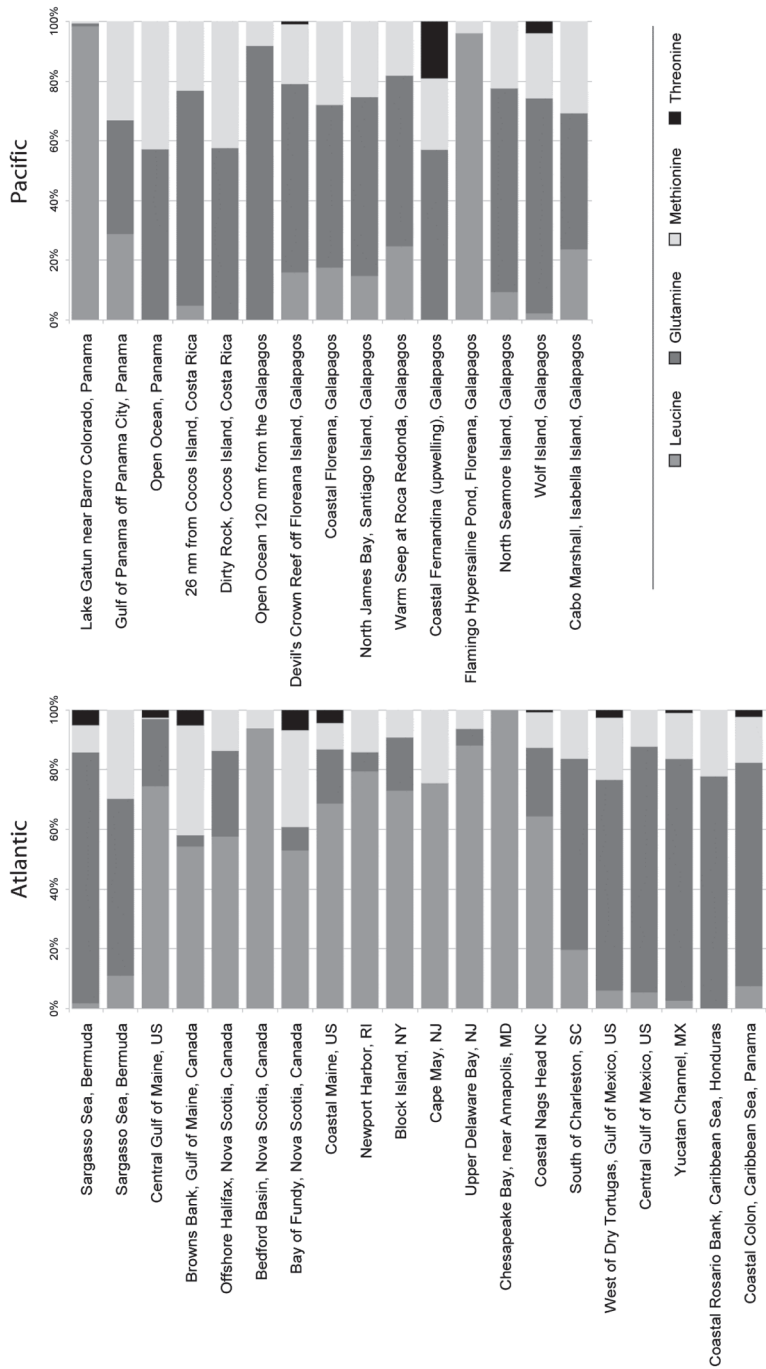


Figure 9.9 Distribution of crucial amino acids in proteorhodopsin populations from different sampling sites indicate different light sensitivities. For details, see text.

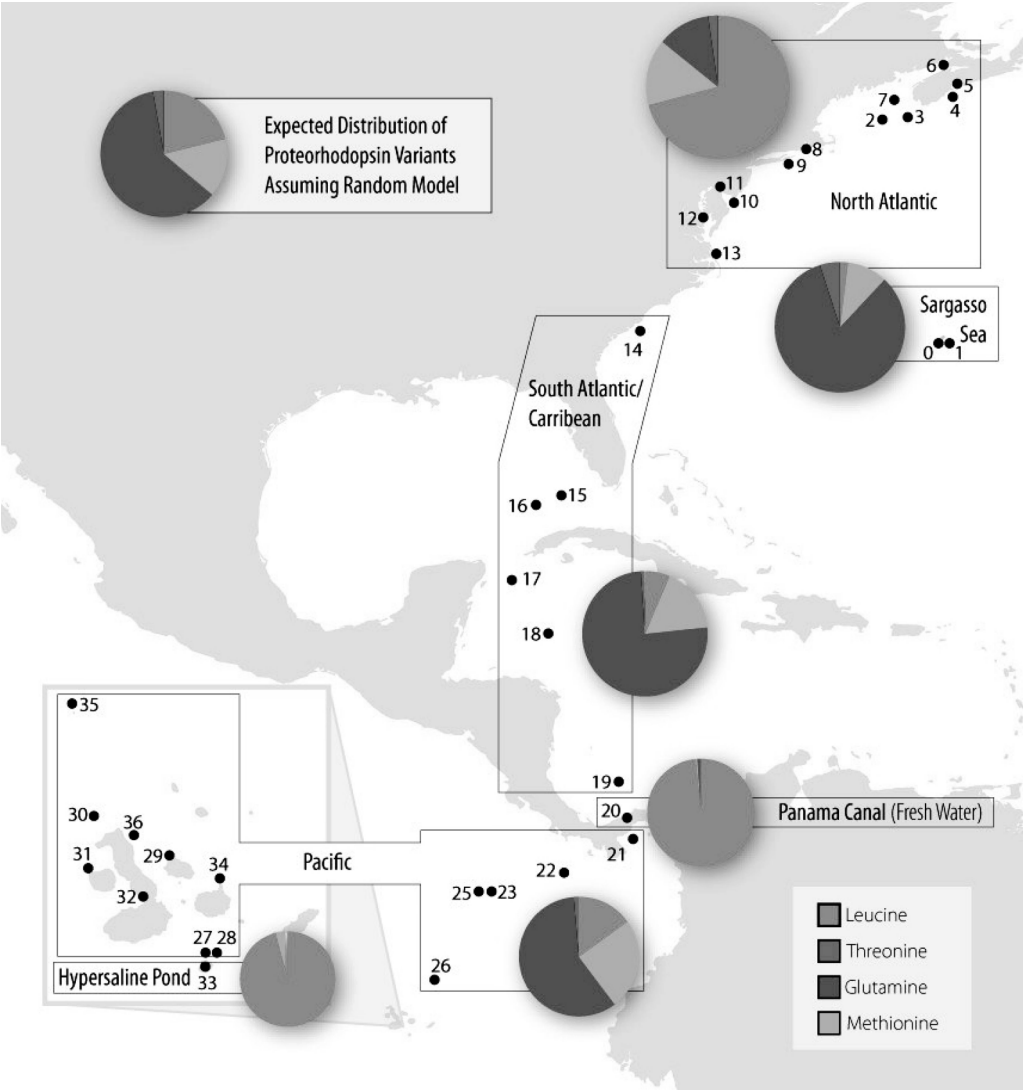


Figure 9.10 Geographical distribution of the predicted proteorhodopsin light sensitivities shows a specific regional pattern.

The amino acid leucine basically codes for a green pigment and glutamine for a blue. Therefore, as one goes from the green North Atlantic down into the Sargasso Sea the water changes color and the pigment associated with the photoreceptors also changes. When we get down to the Panama Canal into fresh water, it is all green, and the saline pond on Floreana Island is all green. Hence not only are the organisms radically different but also the photoreceptors that deal with sunlight distribute in a very unique fashion.

We also find some other rare derivatives that have been found to shift the light into the red. Just by looking at geographic differences with some of the assemblies we can clearly distinguish geographic differences (Figure 9.10), and this has a lot of implications for things such as national security. For example, we think that in a short while, as maps become expanded, it would be very easy to tell where the ballast water in a ship originated from.

The picture of biology, however, is far more complex. Figure 9.11 relates to *Prochlorococcus*. There was a publication 2 years ago of the *Prochlorococcus* genome claiming that it was the most abundant species on the planet, but we have yet to find a sequence anywhere in the oceans that we have sampled that matches the sequence that was taken off Japan. Instead, we find huge clouds of related genes. Each small bar in Figure 9.11 is roughly one gene and we have genes that are highly conserved from organism to organism and stack up as seen in the lower left corner. In addition, there are whole blocks of sequences that are missing in the ocean samples that we have compared with the previously reported *Prochlorococcus* genome. To put things into context, in the past only a small stretch of the genome coding for the ribosomal operon has been used to try and tell all these species apart, data that are 98% identical. With our whole-genome comparison we have identified multiple new clades of *Prochlorococcus* and this is just scratching the surface of what is there.

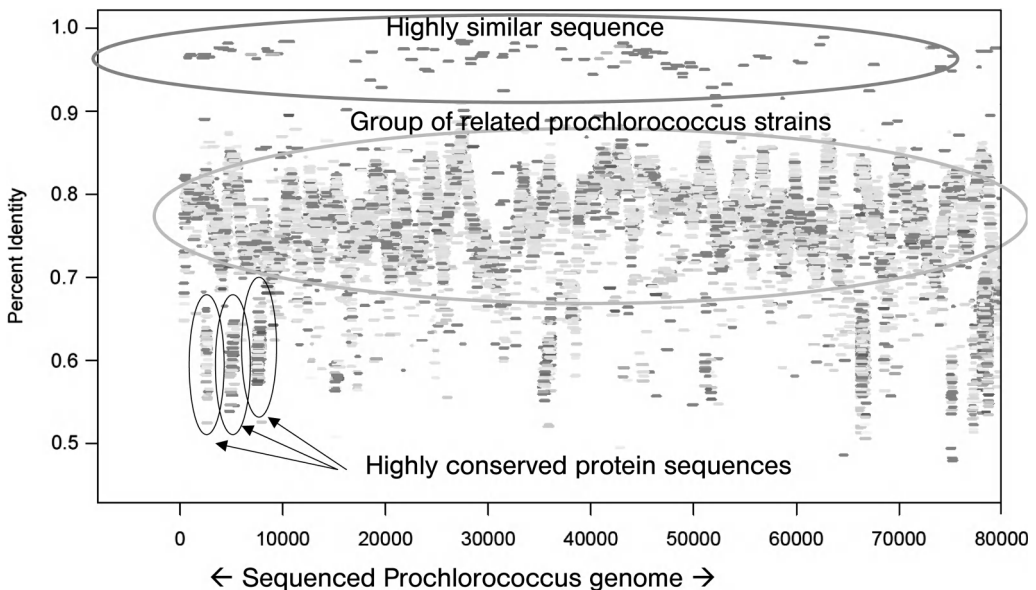


Figure 9.11 Mapping of sequence data to the published *Prochlorococcus* genome shows there are several groups of related, but not identical, strains. Each bar is roughly equal to a single gene.

9.5

Protein Families and Gene Pools

We are trying to answer some principal questions. How many new protein families are we adding, how many distant relatives of known ones?; what is the rate of discovery of new families?; are we close to saturating and understanding the gene pool of the planet? So we have looked at all the data we have to date, namely 17 million open reading frames or genes, and we carried out a computational analysis. It has taken over a 400 000 CPU hours just for the initial computation of taking all these new data from the ocean sampling coupled with all the gene data at GenBank, giving us a total of 29 million genes, and we have been assembling these into gene families (Figure 9.12). Just looking at new gene discoveries, we see that in key areas such as hydrogenases, methylases and cellulases, that have commercial impact, new genes are coming out in abundance from our sampling.

When we look at families with over 50 members at least, we can see that they are still being discovered in an almost linear fashion. When we look at gene families with 10 or more genes, that number comes out between 40 000 and 50 000 and there is no hint of saturation. If we collect 200 000 sequences from a new site, these add on new gene families at this linear rate, which means we are presumably still a very long way from completely understanding the genes on Earth and an even longer way from understanding the majority of biology (Figure 9.13).

When we started this experiment roughly 5000 species of bacteria had been characterized. When one subsequently finds 50 000 new ones in each site, it rather changes the picture. The Gordon and Betty Moore Foundation have funded a microbial genome sequencing project that helped put these data in context and allowed us to sequence and assemble the genomes of up to 130 marine organisms, at a time when there were only 10–20 such genomes known. That meant that in just over 1 year there was a 1000% increase in this type of data. This was a worldwide project with investigators from around the world being asked to nominate genomes, trying to find new things representing diversity to add to the genome databases. It now takes not 13 years as it did with *Escherichia coli* or 4 months as it did with *Haemophilus*, but only about 2 h to sequence each one of these genomes. The sampling sites for the Moore Foundation project were distributed across the world, representing some good diversity on top of the Sorcerer II expedition track.

Sequencing is very expensive, which is why we are trying to find new methods so that we can go back to the sites once we have generated the gene database, for example, looking at microarrays. We also have a collaboration with Affymetrics, which has the ability to put 30 million elements on a chip that we are trying with the environmental data set.

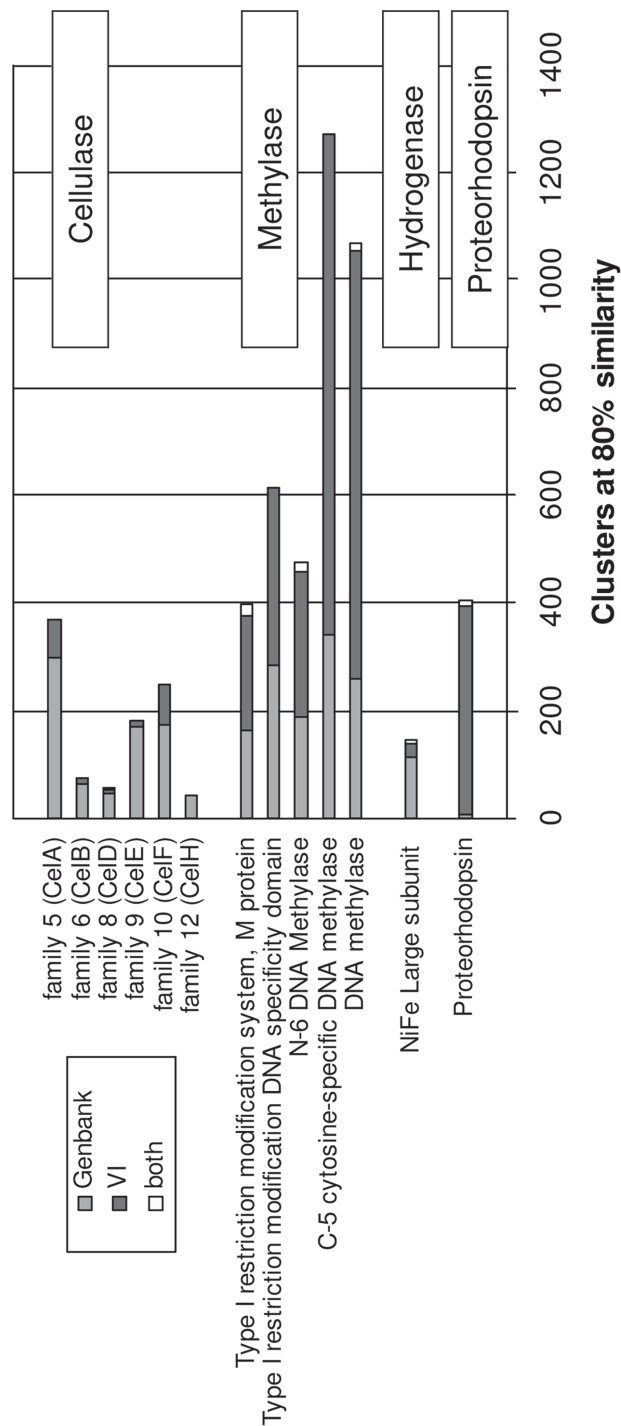


Figure 9.12 Comparison of genes in GenBank (light) with those identified from the Venter Institute (VI) projects (dark) shows that there is only minimal overlap for several important protein families.

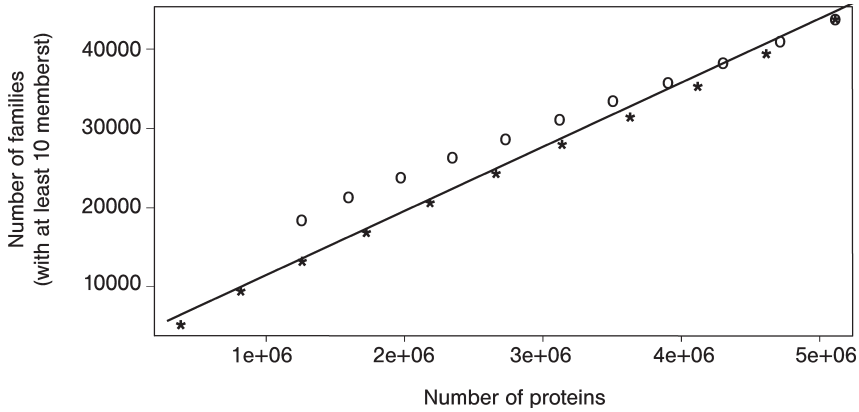


Figure 9.13 Discovery of new protein families, defined as gene clusters with at least 10 members, is a linear function of the number of protein sequences obtained, indicating that there is as yet no saturation due to redundancy in the sequence data.

9.6

The Air Genome Project

In addition to soil and water, we are now carrying out the air genome project with funding from the Sloan Foundation. We are measuring at the tops of buildings in the Washington area and New York for the initial samples (Figure 9.14). We are trying to treat these samples in much the same way as

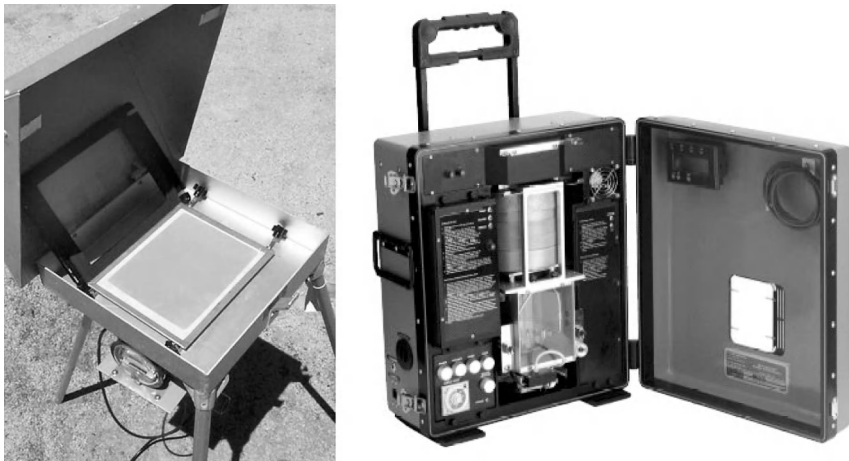


Figure 9.14 Sampling apparatus for the air genome project. Left: Collection of aerosol samples; right: SpinCon wet cyclone sampler.

we did with the ocean samples, although it is slightly more complicated with impact filters. We have also acquired a set of SpinCon wet cyclone samplers, which make the sampling much more similar to what we achieve in ocean sampling, where we have all the organisms in an aqueous form and we just pass them through the same filters as we used for the ocean sampling, and we can therefore fractionate out the eukaryotes from other viruses and single-cell bacteria. The results show that the density and the diversity of organisms that we are breathing every day are really tremendous.

9.7

Conclusion

So, what is the use of this information? We are tracking the various reefs around the world where we have taken the expedition (Figure 9.15). This gives each of the countries a database that they can use for monitoring the changes in reef health. Some studies have shown that just one or two species disappearing can be associated with coral bleaching. One can assess the safety of things such as off-shore drilling, oil spills, where previously we have only been able to measure what happens to large mammals. We can monitor drinking water safety, tracking ballast sources, and now, with the air genome project monitor, air quality and safety, and we have a major program with various countries in Asia trying to track the emerging viruses, attempting to help prevent a pandemic.

The expedition is now on its way from Australia to Africa, collecting samples every 200 miles along the way, and will be ending by the end of 2005. To cope with data from this first round with over 300 sites, we are having to use the largest government computers, and we are also getting help from Google who have even larger computers to analyze all these data. Our website, Sorcerer2expedition.org, provides information about the boat, the sites, the data that have been posted so far and future data as they are published. We hope that as we continue on, we will leave a lot of exciting new data in our wake.

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Key Messages

Author Biographies

Rita Colwell



*Former Director, National Science Foundation;
Distinguished Professor, University of Maryland & the Johns Hopkins University*

Dr. Rita Colwell is Chairman of Canon US Life Sciences, Inc. and Distinguished University Professor both at the University of Maryland at College Park and at Johns Hopkins University Bloomberg School of Public Health. Her interests are focused on global infectious diseases, water, and health, and she is currently developing an international network to address emerging infectious diseases and water issues, including safe drinking water for both the developed and developing world.

Dr. Colwell served as the 11th Director of the National Science Foundation, 1998–2004. In her capacity as NSF Director, she served as Co-chair of the Committee on Science of the National Science and Technology Council. One of her major interests include K-12 science and mathematics education, graduate science and engineering education and the increased participation of women and minorities in science and engineering.

Dr. Colwell has held many advisory positions in the U.S. Government, nonprofit science policy organizations, and private foundations, as well as in the international scientific research community. She is a nationally-respected scientist and educator, and has authored or co-authored 16 books and more than 700 scientific publications. She produced the award-winning film, *Invisible Seas*, and has served on editorial boards of numerous scientific journals.

Before going to NSF, she was President of the University of Maryland Biotechnology Institute and Professor of Microbiology and Biotechnology at the University Maryland. She was also a member of the National Science Board from 1984 to 1990.

Dr. Colwell has previously served as Chairman of the Board of Governors of the American Academy of Microbiology and also as President of the American

Association for the Advancement of Science, the Washington Academy of Sciences, the American Society for Microbiology, the Sigma Xi National Science Honorary Society, and the International Union of Microbiological Societies. She is a member of the National Academy of Sciences, the Royal Swedish Academy of Sciences, Stockholm, the American Academy of Arts and Sciences, and the American Philosophical Society.

Dr. Colwell has also been awarded 45 honorary degrees from institutions of higher education, including her Alma Mater, Purdue University. She is an honorary member of the microbiological societies of the UK, France, Israel, Bangladesh, and the U.S. and has held several honorary professorships, including the University of Queensland, Australia. A geological site in Antarctica, Colwell Massif, has been named in recognition of her work in the polar regions.



Michael Osborne

Director, Multi-Disciplinary Issues, International Futures Programme, OECD

Michael Osborne has been at the Organization for Economic Co-operation and Development (OECD) since 1980. He has held posts as Senior Research Fellow (China and Pacific Basin), Executive Assistant to the Deputy Secretary General of OECD, Head of the Science and Technology Policy Division of OECD, and Deputy Director for Science, Technology and Industry. He is presently Director of Multidisciplinary Issues in OECD and Director of the OECD's International Futures Programme. He is also Director for the OECD's Global Science Forum.

Dr. Osborne was educated at the University of California at Berkeley (BA, MA, and PhD), Cambridge University, and the Ecole Normale Supérieure in Paris. He has taught at universities in the United States, Great Britain, France and Italy (as a Senior Fulbright Professor). In the 1980's he worked on the political economies of the Pacific Basin countries, and published books and articles on technology and direct foreign investment issues in the People's Republic of China.

Over his career, Dr. Osborne has worked extensively in the areas of biotechnology, science policy, innovation policy frameworks, information technology policy and the political economy of China. Currently, the International Futures Programme is working on projects focused on the commercialization of space, the new security economy (particularly biosecurity issues), monitoring and managing new systemic risks and the emerging bio-economy. He chairs the OECD Internal Coordinating Group on Biotechnology.



Feike Sijbesma

Managing Board of Directors, DSM; Chairman, EuropaBio

Feike Sijbesma studied medical biology at the University of Utrecht, The Netherlands, and business administration at Erasmus University in Rotterdam. In 1987, he joined the Industrial Pharmaceuticals division of Gist-brocades, where he was responsible for strategic planning and business development. From 1990 to 1993, he was appointed the division's Marketing and Sales Director. Thereafter he was given leadership of Savoury Ingredients, later on a business unit of Gist-brocades' Food Specialties Division. In 1995, he was made director of that division and joined the Gist-brocades' Executive Committee. In 2000, Mr. Sijbesma joined DSM's Managing Board of Directors.

Supervisory directorships and other positions held:

- Chairman of the Board and the Executive Committee of EuropaBio (European Association for Biotech Industries)
- Board member of the Wageningen Centre for Food Sciences (WCFS)
- Member of the Supervisory Board of Utrecht University
- Member of the Supervisory Board of the Dutch Genomics Initiative
- Chairman of the Dutch Food Chain Sustainability Foundation (DuVo)

Synthesis and Recommendations

Rita Colwell, Michael Osborne, Feike Sijbesma

1

The Rationale Behind White Biotechnology

What is the rationale for applying white biotechnology?

Global trends such as urbanization, industrialization, increasing consumption, unstable oil & gas markets put environment, health and society under pressure by increasing

- degradation of natural habitats
- global warming
- environment-associated diseases
- depletion of fossil resources.

To cope with these pressures we need more sustainable industrial production.

White biotechnology has already provided benefits along the triple P of sustainability:

- *Planet*: less fossil resources, less emissions, less energy.
- *People*: better quality of life, rural development.
- *Profit*: lower cost, innovative new products, jobs.

2

The Situation Today

Where do we stand today in the use of white biotechnology processes?

- Already today industrialized countries benefit from white biotechnology in many different ways, e.g., by producing:

- *Biofuels*: 1–2% of transportation fuel needs are met through bio-ethanol & bio-diesel, the sector is growing by 20% annually, and the first biomass-to-fuel plant is in operation.
 - *Biomaterials*: The first biodegradable plastics from renewable raw materials are on the market at competitive cost and are used for, e.g., packaging.
 - *Biochemicals*: Selected chemical syntheses (e.g., vitamins and antibiotics) have been transferred to cleaner and cheaper bioroutes.
 - *Bioactives*: Enzymes contribute to many “green” processes and better products (e.g., detergents, paper, textiles, food, feed and bioremediation) saving approx. 20 megatons in CO₂ emission annually.
- In terms of economic importance, approx. 3–5% of chemical production is now based on white biotechnology.
 - There has been tremendous progress in basic science and technologies, but continued investment is required in particular towards economical applications.
 - In terms of public acceptance, there is increasing support from consumer and environmental organizations (e.g., German Green Party, NRDC), but the lack of general understanding is not to be underestimated.
 - Substantial regulatory hurdles remain especially in EU (e.g., long approval times, high sugar costs because of market protection).
 - Significant industrial activity is seen around profitable incremental applications, but investments in long-term breakthrough technologies need more stimulation.
 - Developing countries are struggling with access to intellectual property (patents) and to raise funds to adapt and apply technologies locally.

3

The Concerns

What are the chief concerns expressed about white biotech?

- Scarce land and water has to be used for large scale bio-based production.
- A high level of containment of genetically modified microorganisms must be ensured to prevent their uncontrolled release into the environment.
- There is currently an insufficient return on investments.
- The inequalities between developed and developing countries may be increasing through white biotechnology.

4

The Future

Where do we want to be in 10–20 years?

- White biotechnology will be incorporated into societal activities and contributing to science and industry.
- The benefits of a bio-based economy will be maximized:
 - Biofuels play a significant role in the energy mix especially through cellulosic biomass conversion that is not competing with food.
 - Industrial processes are switched to bioroutes and biorefineries where it makes economic and environmental sense.
 - Innovative bioproducts provide new benefits to consumers, e.g. in healthcare ingredients, improved detergents, biodefense.
 - White biotech applications will have been invented and adopted into industry, health and environment in developing countries.
 - Exploration of biodiversity and symbiosis with other technologies, e.g., nanotech, agricultural science, information technology, allows to take advantage of new discoveries.
 - We will have a better understanding of biocomplexity and complexity of ecological systems.
- White biotechnology will have a significant contribution to improving environment and health.
- Continued investment in basic research will facilitate new discoveries.
- Private and public investments in application & product development will increase.
- Industry will take the lead by actively searching and pursuing existing opportunities, rather than following a “wait and see” approach.
- Political leadership and support for appropriate regulatory and economic conditions will be available, acknowledging that benefits materialize over the longer term.
- Risks and benefits of new technologies will be balanced.
- Public debate involving citizens on all levels will be encouraged, using multiple approaches for educating the public, and focusing on tangible and meaningful arguments.